

An Interpretation of Diabetes in the Light of its Pathology

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Last year the Banting Memorial Lecture was given by a man preeminently qualified, Dr. Charles H. Best, Doctor Banting's co-worker and one of the world's leaders in physiology and in knowledge of diabetes. My own claim is nebulous—a medical student who saw Doctor Joslin treat one of the first patients in the United States to receive insulin, a young doctor who admired Doctor Banting for his work and for his kindness to his visitors, a pathologist inspired to study diabetes by Doctor Joslin's insight and enthusiasm.

Last year Doctor Best told you of the discovery of insulin, of its nature, of its action. This year I wish to present to you the effects of insulin insufficiency.

LESIONS OF THE ISLANDS OF LANGERHANS

The diabetic process is most often associated with lesions of the islands of Langerhans. Since Opie's¹ demonstration of hyalinized islands (Figure 1) as the typical lesion in diabetes, the list of pathologic changes has lengthened; the instances of apparently normal islands in diabetic patients have become fewer as our technics have improved. Not only is this true in man, but also in spontaneous diabetes in animals. As more and more ways of producing experimental diabetes are found, the islands in the animals made diabetic tend to show pathologic changes.

Although the adrenals^{2,3}, the pituitary gland⁴⁻⁷, the liver⁸ and other organs play a significant and sometimes vital role, the pancreas is still the key organ in both clinical and experimental diabetes; the islands, and

especially the beta cells^{9,10}, are the essential units through which the functional change is mediated. Nonetheless, apparently normal islands are present in some cases of diabetes.

The beta cells in the islands, the source of insulin, predominate and are closely associated with the rich network of insular capillaries. The alpha cells are normally less numerous, and in man tend to be at the periphery of the islands. Loss of beta granulation, followed by hydropic degeneration, may be reversible changes in the experimental animal, but when seen in man usually indicate a rapidly developing or uncontrolled diabetes. Toreson¹¹ has demonstrated that in some instances, at least, the "hydropic" vacuoles contain glycogen. In my experience, hydropic degeneration is rare in the insulin-treated diabetic.

The metabolism of the beta cell, as suggested by Lazarow¹², is largely dependent on cysteine. Insulin is 12 per cent cysteine, probably formed by oxidation of cysteine. Alloxan may act by interference with this mechanism.

The persistence of uninjured alpha cells in the islands, (Figure 2) and their increased proportion in many suffering from diabetes, has led to the belief that they may produce a substance that enhances diabetes¹³; however, selective destruction of alpha cells does not permanently alter an experimental diabetes¹⁴.

All interested in diabetes know of the injurious effect of alloxan on the beta cells; fewer are acquainted with a substance that damages alpha cells almost as specifically, cobalt chloride^{15,16}, or ethionine^{17,18}, which kills the acinar cells.

Now that insulin is commonplace, it is easy to forget the proteolytic enzymes of the acinar cells long delayed its discovery. An illustration in a paper by Moses Barron¹⁹ of a pancreas devoid of acinar cells, but with its islands intact, was the clue that started Banting on

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his work that resulted in the ready availability of insulin. Now, of course, through the brilliant work of Banting, Best and their colleagues, insulin can be extracted from the whole pancreas, rather than from the pancreas of dogs, whose acinar cells are largely destroyed by duct ligation.

Hyaline deposition in the islands has long been considered the classic lesion in diabetes. Deposition is largely restricted to the islands and spares the acinar tissue. The hyaline is related to amyloid, and may well represent deposition of a polysaccharide-protein complex from the blood. It is always in close relation in the insular capillaries²⁰.

A rare lesion, most often seen in children suffering from infectious disease as well as diabetes, is lymphocytic infiltration of the islands, probably a sequel to gradual necrosis of the epithelium. This may be followed by scarring and fibrosis, lesions which may give no clue as to their origin.

What amounts to a diabetes of known etiology exists in man. This is hemochromatosis, basically a disease caused by failure to metabolize iron properly. Hemosiderin accumulates in various of the tissues, usually appearing first in the liver. Only when the process extends to the pancreas and involves a sufficient number of the islands of Langerhans will diabetes develop. The islands may be more or less damaged and sometimes show evidence of regeneration. As the iron is laid down, it eventually so disturbs the metabolic activity of the cell that life is no longer possible. When enough beta cells are damaged in this way, diabetes develops. The typical syndrome of bronze diabetes is then seen: enlarged liver due to the piling up of iron, the death of liver cells, regenerative activity and cirrhosis; diabetes following excess storage of iron in the pancreas and loss of beta cells; bronze pigmentation of the skin, related in part to deposit of iron pigment in the structures of the skin, in part to deposition of iron in the cortex of the adrenal which leads to a disturbance of melanin pigmentation. The severity of the diabetes increases with the amount of damage done to the islands of Langerhans.

ABNORMALITIES IN GLYCOGEN DEPOSITION

The solubility of glucose makes it impractical to demonstrate it by histologic means. However, its polymers, and particularly glycogen, can be demonstrated. The liver of a normal individual contains a large amount of stored carbohydrate in the form of glycogen. The untreated diabetic usually has a badly depleted store

of glycogen with very little present in the cytoplasm in the liver cells, and only a moderate amount stored in their nuclei. Adequate glycogen in the liver cytoplasm means for the diabetic patient that he has an adequate store of carbohydrate in shape for metabolic use.

In pre-insulin days, the characteristic lesions of the diabetic patient were the disturbance of the glycogen deposition and changes in the islands of Langerhans. There was depletion of glycogen from its normal stores and excess glycogen in the cells where it was not normally stored, or in parts of the cell where it was not normally stored, as the hepatic nuclei, proximal convoluted tubules, and Henle's loops. Now, with better control of the diabetic patient, we find a normal or more nearly normal distribution of the glycogen.

PATHOLOGIC CHANGES IN THE KIDNEYS

Other less frequent but characteristic changes are seen, such as the presence of a peculiar hyaline material usually occurring in masses in the glomeruli of the kidney, usually deposited toward the outer portions of the tuft at first, but finally occluding the entire tuft. (Figure 3) This material, first described by Kimmelstiel and Wilson²¹, stains by histochemical technics, as would either a glycoprotein or mucopolysaccharide. Both afferent and efferent arterioles may show hyaline thickening of their walls, with similar material.

As seen under the Polaroid ultraviolet color translation microscope, this hyaline differs from that seen in glomerular nephritis or arteriosclerotic lesions. The process is not always clear-cut and distinctive, as in many diabetic patients one finds that there are other complicating lesions in the kidney. Thus the Kimmelstiel-Wilson change may coexist with a characteristic arteriosclerotic change in the glomeruli or a chronic pyelonephritic process. As illustrated in Figure 4 nephropathy is now very important as a cause of disability or death in the diabetic patient.

INFECTIONS

Infection, aside from renal infection, is no longer the risk for the diabetic patient that it used to be, although one must still keep in mind that with every infection there will be marked lowering of the sugar tolerance and increase in the insulin requirement. Today, staphylococcal infections, such as extensive carbuncles of the neck, are rarely seen in the diabetic thanks to sulfonamides, antibiotics, and better care.

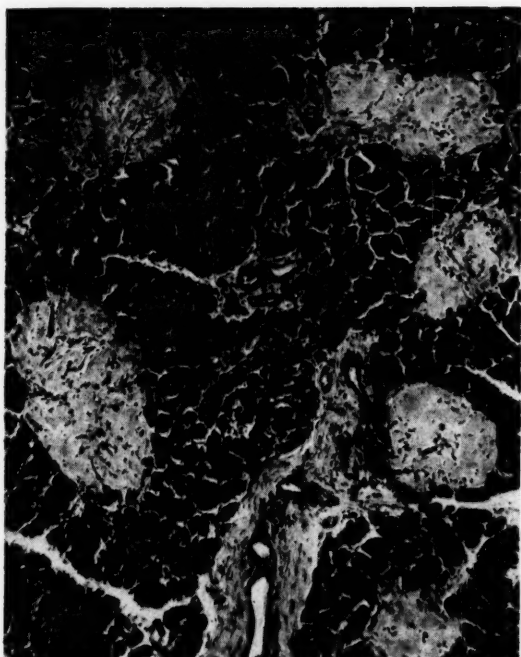


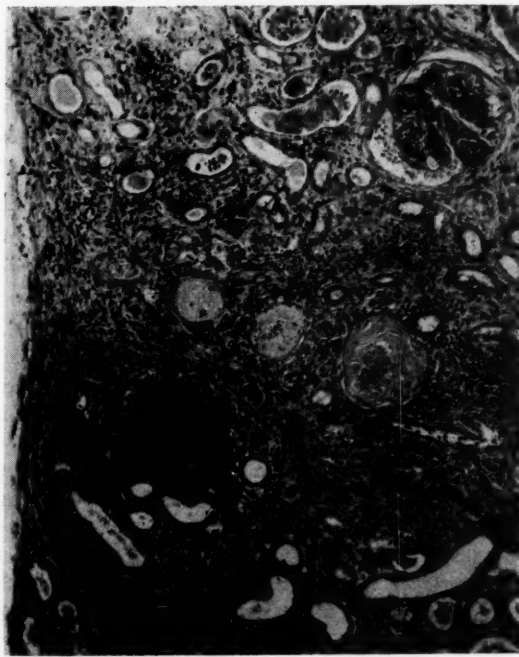
FIGURE 1 (Above) Hyaline islands in diabetes. (X 125).

FIGURE 3 (Below) Hyaline material within renal glomeruli in Kimmelstiel-Wilson disease. (X 300).



FIGURE 2 (Above) Island of Langerhans of alloxan-treated rabbit showing chiefly alpha cells. (X 400).

FIGURE 4 (Below) Concurrent chronic pyelonephritis, arteriosclerosis and Kimmelstiel-Wilson disease in diabetic nephropathy. (X 140).



MANIFESTATIONS OF LIPOID DISORDERS

Lipoid disorders occur, of course. Some are relatively unimportant to the welfare of the individual, such as the characteristic xanthomas which may appear on the skin of the diabetic patient, usually about the larger joints. This is a reversible process in distinction to the laying down of the cholesterol and associated lipids in the arteries where the process is an irreversible one.

ARTERIOSCLEROSIS

Vascular damage is still very important to the diabetic patient. Arteriosclerosis in the diabetic differs in severity, in the topographic distribution, and in onset at an earlier age than arteriosclerosis in the nondiabetic. One cannot look at an artery and say positively that this is the artery of a diabetic patient or that this is the artery of a nondiabetic patient. On the other hand, if one has a patient in whom there is extensive involvement of the muscular arteries with the atheromatous type of process rather than medial calcification, one can say this is probably a diabetic. Also, if one finds a marked degree of atheromatous arteriosclerosis in a younger person, the probability is very strong that the patient has diabetes. The rapidity with which cholesterol can be laid down is illustrated by a recent observation by Duff²³ and his colleagues at McGill University, who have found that there may be demonstrable amounts of cholesterol esters laid down in the arterial wall of the rabbit four hours after feeding of cholesterol has been started. This is without change of the endothelial cells themselves and represents passage of the cholesterol and cholesterol esters through those endothelial cells into the ground substance of the intima of the aorta.

Seventy-five per cent of this recent study of diabetic mortality showed arteriosclerosis as a cause of death. The coronary artery is all too often involved, with lumen narrowed by atheromatous plaques with or without calcification, and the residual lumen may be occluded by a thrombus. This is apt to be a gradually evolving process, rather than a steadily developing one, as is shown by some cases in which multiple occlusions occur. In these cases, the coronary circulation, as demonstrated by Schlesinger's method of injection of the coronary system with a radio-opaque material, and x-ray examination, shows multiple occlusion of the coronary vessels.

DIABETIC RETINOPATHY

The microaneurysms of retinal vessels are all too characteristic a change in the diabetic patient. These microaneurysms have been shown by Friedenwald²⁴ and others to develop following deposition in the vessel walls much the same type of mucopolysaccharide that is seen in the kidney in Kimmelstiel-Wilson disease, and LeCompte and I have been inclined to think that many of the complications of the diabetic patient related to the hyaline alterations in intercellular substance such as this, such as the change in the renal glomeruli, such as the changes in the smaller blood vessels, such as related to the hyaline laid down in the islands of Langerhans, may well be related to an excess formation of a mucopolysaccharide and its resultant laying down in relation to the walls of the smaller blood vessels. In this way, one can conceive of the diverse pathologic processes related to small vessel damage as being essentially a single process varying more in topographic location than in the underlying change.

The veins can be involved in the deposit of this hyaline-like material, as well as other portions of the circulatory system. One sees this same material that stains as a mucopolysaccharide laid down.

Retinitis proliferans may be a disastrous complication for the diabetic patient. This is essentially an organizing process, new capillaries being formed, new fibrous tissue being laid down, following small hemorrhages.

CAUSES OF DEATH IN DIABETES

Doctor Joslin's meticulous study of his patients provides me with data²² as to the causes of death in his patients as experienced in 1950, 1951, 1952 and 1953 up to May 5 (Table 1). Of 1,358 deaths, coma caused only 1 per cent. Diabetic nephropathy caused 9.2 per cent. Forty-seven per cent of the deaths were cardiac, chiefly coronary in type. Acute infections caused 5.6 per cent, and tuberculosis caused 1 per cent, while cancer was responsible for 10 per cent. Gangrene dropped to only 1 per cent. Thirty-five per cent of these patients had lived with diabetes twenty years or longer, and the average duration was 16.3 years.

Sometimes acute pyelonephritis in the diabetic patient may be extreme, with the whole surface of the kidneys flecked with the multiple abscesses that characterize the process, and on section virtually all of the parenchyma has been replaced by multiple abscesses with only little patches of fairly normal tissue persist-

TABLE 1. The Causes of Death of Diabetic Patients, 1950-1953*; Experience of the Joslin Clinic, Boston, Mass.

Cause of Death	Number of Deaths	Per cent of All Causes
All Causes	1,358	100.0
Diabetic Coma (Primary)	14	1.0
Cardio-renal-vascular	1,027	75.6
Arteriosclerotic	1,020	75.1
Cardiac	640	47.1
Coronary and Angina	453	33.4
Renal, total	167	12.3
Diabetic Nephropathy	125	9.2
Typical or Unqualified**	107	7.9
Probably	18	1.3
Cerebral	166	12.2
Gangrene	18	1.3
Site unassigned	29	2.1
Other circulatory and rheumatic heart disease	7	0.5
Infections, total	76	5.6
Pneumonia and respiratory	54	4.0
Gall bladder	4	0.3
Appendicitis	1	0.1
Kidney, acute	5	0.4
Abscesses	1	0.1
Other infections	11	0.8
Cancer	136	10.0
Tuberculosis	13	1.0
Diabetes—(i.e. unknown)	14	1.0
Accidents	22	1.6
Suicides	4	0.3
Insulin reactions	3	0.2
Other diseases	49	3.6

*Deaths reported through May 5, 1953

**36 confirmed by autopsy

ing. This can sometimes go on to the very extreme lesion of the necrotizing papillitis, where the papillae are in many instances completely necrotic. The tip of a pyramid with its collecting tubules may become entirely necrotic and sequestered from the rest of the kidney.

SUMMARY

These are examples of the various types of pathologic change seen in the diabetic patient, both as they occurred in the past and as they now occur. There are two important concepts to keep in mind: (1) The diabetic process is most frequently associated with damage to the islands of Langerhans. While in some instances normal islands still are found, it may be that they appear normal simply because of the imperfections of our technic. (2) The vascular damage, varied as it is, is related on the one hand to cholesterol and cholesterol esters, and on the other hand to the changes in the ground substance that results from the accumulation in the vessel wall of the complex combination of protein and carbohydrate that we called mucopolysaccharides or the glycoproteins. Whether one is dealing with a

damaged retina or damaged kidney, whether one is dealing with a damaged heart or a gangrenous leg, the basic processes that have taken place in the vessels are quite closely related to one another.

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Treatment of Diabetes

Selection of Technic according to Severity

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The following doctrines are fundamental in current understanding and treatment of diabetes mellitus. They are accepted and employed by the great majority of informed physicians in this country.

Almost all human diabetes is idiopathic, in the present state of knowledge. In some instances it has a demonstrable organic cause, or is intensified by one. When this is true, and when the cause can be removed or relieved, that should be done, of course. When there is no demonstrable cause supportive treatment must be used. Normal behavior can be attained in the majority of cases by proper use of such measures. When it cannot, it should be approximated as closely as is feasible in the individual case.

Supportive methods of treatment now consist, for the main part, of limitation of the food supply, with or without the daily use of insulin, as required by the individual patient. Adjunctive measures include regulation of physical exercise, reduction of excess weight, and elimination of infection and other physiologically abnormal states such as emotional stress.

In this review of therapy it will be assumed that organic factors and adjunctive measures are appreciated, and that nutritional rules are understood and applied. The chief objective here will be a correlation of different grades of severity of diabetes with the most effective methods of treatment for each. Selective therapy with diet and insulin is the intention.

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Intelligent selection of available methods can be made only in the light of certain beliefs and zones of knowledge. Probably the most important of them are:

1. Confidence in the precept that freedom from glycosuria and hyperglycemia is desirable whenever feasible.
2. Some ability to judge grades of severity in different patients with diabetes.
3. Appreciation of the characteristic diabetic responses to food intake, particularly of carbohydrate.
4. Knowledge of the relative timing and dosage characteristics of insulin and its various modifications.
5. Observation of individual responses to prescribed treatment, for the purpose of making appropriate adjustments when required.

The first and last of these principles will be taken for granted in this review. We will be concerned chiefly with the needs of different types of diabetes for various forms of food and insulin therapy.

SEVERITY OF DIABETES

If, at one extreme, the normal, nondiabetic person is considered thoughtfully, and, at the other, the "total" diabetic, the range of possible variations in severity may be visualized. In the normal, automatic mechanisms insure proper food utilization ("homeostasis"—Cannon). No diabetes exists and no treatment is required.

As the opposite extreme is approached, more and more of the capacity for automatic utilization of sugar (and other related metabolic substances) is lost until none remains. The diabetic becomes more and more dependent on administered treatment. When all homeostatic reserve is lost and total diabetes ensues, he becomes completely dependent upon outside manipulations and, like a depancreatized animal, cannot stay alive very long without them. Faults in these manipulations then become evident, after having been concealed in less severe diabetes by some reserve ability to adjust automatically.

Violent shifts in balance occur on slight provocation, towards glycosuria and acidosis or towards insulin shock, whenever relative deficiencies or excesses of insulin effect appear. In describing the ease with which balance may be lost and damage occur, the severe diabetic can be compared to a tight-rope artist, and the mild diabetic to the person who walks on a wide path.

What does this concept imply in terms of applied treatment? Simply this: if a balanced state of metabolism is to be maintained, more and more skill in manipulation (of food and insulin, particularly) will be required as more and more severe diabetes is manifest. This is true both for physician and patient. To escape harm due to uncompensated changes, a good balance between insulin effect and food supply at all times of day will be required. As stated above, this involves some ability to judge severity of diabetes, and some knowledge concerning the effects of food and various insulins in diabetes.

Too often the size of the daily insulin dose is used as a measure of the severity of diabetes. This standard is acceptable only in the average case. Many exceptions occur, due to individual variations in *insulin sensitivity*, which have little to do with inherent *severity*. It is not safe to judge the individual patient by the amount of insulin required, even though the majority do conform crudely.

As the study of the individual patient proceeds, the following important aids in estimating severity appear and become useful as guides to treatment. All of them appear earlier, and are more important, than the size of the insulin dosage required.

1. *Age of patient at onset of diabetes, and its duration.* Exceptions occur, of course, but a useful generalization, particularly for young people, is found in the fact that the earlier in life diabetes makes its appearance, and the longer it has existed in any individual case, the more severe it is likely to be.

2. *Intensity of diabetic symptoms and signs without treatment.* An approximate indication of severity is furnished by the rate of weight loss (without diet restriction), amounts of diuresis and thirst, history of ketogenic acidosis, and blood and urine sugar levels in relation to amount of food eaten.

3. *Thinness accompanies severity and obesity mildness,* as a rule. Notable exceptions are the young, severe diabetics taking large amounts of insulin who become obese because they eat too much.

4. *Ease and speed with which glycosuria and acidosis can occur.* In the same individual, usually this is pro-

portional, also, to the ease with which insulin reactions can occur, and the violence of the resulting shock. Both phenomena reflect relative failure of mechanisms which compensate homeostatically, thus indicating degree of diabetes, by definition. These behavior characteristics are probably the most reliable indicators of severity available.

Criteria such as these, when considered along with the amount of insulin required and the apparent sensitivity of the individual response to insulin, usually provide a dependable estimate of the degree of diabetes present. To the extent that they do, they furnish valuable hints as to the best uses of food and insulin in treatment.

Assuming positive identification of diabetes, two large groups of about equal size coexist, one composed of patients with mild diabetes manageable by diet, the other with more severe diabetes which requires insulin. Both may become complicated by acute illness and require emergency methods of management. Table 1 summarizes the characteristics of each group and subgroup, referring to the food and insulin methods which have been found most useful in each.

TABLE 1 Varieties of Diabetes Mellitus and the Therapeutic Methods Most Appropriate for Each.

Severity and Incidence	Common Characteristics	Most Appropriate Treatment
Manageable by Diet Mild 40 to 50% of Total	Elderly adults. Obesity common. Symptoms absent or negligible.	Desugarization by diet restriction. Weight control. No insulin, or temporarily at most.
Requiring Insulin a) Moderate 20 to 30%	Onset middle life and later. Early in young. Control easy.	Any depot insulin in moderate dosage. Often insensitive to insulin.
b) Severe 10 to 20%	Long duration in adults. Many juveniles. Responsive to minor influences. Balance shifts easily.	Intermediate insulins once daily (Globin, NPH and mixtures).
c) Labile 10 to 20%	Most children and juveniles, some adults. Chronic infections. Acidosis on slight provocation. Sensitive to insulin, with unpredictable reactions.	Intermediate insulins twice daily. Some glycosuria condoned. Interval feedings. Avoid reactions. Watch for ketonuria.
Acute Complications. Possible in all	Acute infections. Acidosis—any degree. Trauma. Surgery. Other acute illness.	Plain insulin. Frequent injection. Frequent tests to determine response. No reliance on depot insulins.

MILD DIABETES

Diabetes not so severe as to require insulin is found most often in elderly persons but it may be mild early in its course in the young. Obesity is frequent, sugar levels usually are moderate or low, and symptoms not pronounced.

Management of this type of diabetes by diet alone involves three important principles. Their application imposes minimum burdens, often improves the diabetic process, and is perfectly safe in the absence of complications. They are: (a) desugarization; (b) maintenance of a "sugar-free" state as a habit; and (c) control of excess weight.

Desugarization. If possible by diet at all, desugarization can usually be accomplished within a week or so. In borderline cases it may take longer. Sharp restriction of food intake is essential. The less the supply the better are the chances of desugarization. Undernutrition is not usually harmful, for short periods, and may serve an important purpose, as Allen showed before insulin was available. Short periods of ketosis and negative nitrogen balance are not dangerous, as a rule, although most modern students would agree that they are undesirable and unnecessary.

In the absence of acute complications the effort to desugarize by diet should be continued as long as blood and urine sugar levels fall towards normal. If minimal diets are used, stability at hyperglycemic levels is a positive indication for insulin, temporarily at least. A fair number of mild diabetic patients then will desugarize with insulin, later remaining sugar-free without it for various reasons.

Otherwise, the temporary use of insulin solely for desugarizing purposes is not recommended. It prevents the accumulation of useful knowledge about the response to diet, is undesirable psychologically, and saves no time, because the effect of stopping it remains to be determined.

Control. The habit of keeping "sugar-free" should be encouraged. This is the best way to preserve health, prevent complications, and live simply in spite of diabetes. Occasionally it results in the disappearance of all signs of the disease. The principle involves firm indoctrination of the patient; familiarity with food values; amounts and substitutions; and systematic testing to determine state of control. Routine records, visits and reports to the physician are potent stimuli for consistency and advanced learning in these respects.

Weight reduction. Excess weight should be lost promptly and its return prevented by caloric restriction. Strict control of fat intake is the most effective way to accomplish this. Persistency is the secret of success.

Inasmuch as most individuals with mild diabetes are obese, and in them weight loss due to diabetes has not been pronounced, the principle of weight control finds its widest application here. Where obesity exists or tends to occur in severe diabetes, however, the principle is equally important. Control of diabetes with insulin is desirable, but even more so is improvement in the inherent severity of the underlying diabetes. That can often be accomplished by weight reduction, as well as it can by consistently good control of abnormal hyperglycemia and glycosuria.

SEVERE DIABETES

The apparent number of severe diabetics who need insulin depends upon individual standards of treatment. Liberal use of carbohydrate creates the need for insulin more frequently than moderation, and strict chemical criteria for control more frequently than condonement of abnormal hyperglycemia and glycosuria. Conservatively, diabetes severe enough to require insulin routinely is estimated at about one-half of the known diabetic population (Table 1). Three increasing grades of severity exist within this group, each recognizable by the ease with which the diabetes can be controlled by insulin. By "ease of control" we mean the ease with which abnormal glycosuria, hyperglycemia, and unpredictable hypoglycemic symptoms can be prevented under routine conditions of dietary and insulin therapy.

Moderate. As indicated in Table 1, the most common of these three grades is found in older people, or else early in the course of the disease in the young. Symptoms have not been prominent, weight loss has been absent or moderate, and acidosis infrequent. Many patients are obese and have hypertension. They are troubled more by vascular disease, chronic infections and laboratory reports than by the nutritional and metabolic effects of their diabetes. Fasting blood glucose levels usually do not exceed 300 mg. per cent nor glucose excretion 50 grams daily.

Diabetes of such a moderate grade of severity can be balanced easily with almost any type of depot insulin given once daily, in moderate dosage as a rule. A fair reserve of ability to adjust sugar levels automatically still remains. Minor discrepancies in insulin timing, food supply, exercise and other influences are not reflected as

large waves of hyper- or hypoglycemia. An approximate balance, with the help of a little insulin effect, is all that is required. The gentle action of the slow, weak insulin preparations is quite appropriate, therefore, and protamine zinc insulin (Figure 1) is usually employed. Intermediate-acting insulins are fully as effective, even so, and only one injection daily of plain or crystalline insulin may provide good control without reactions in some of the milder cases. Practically any type of insulin will fill the needs of these patients.

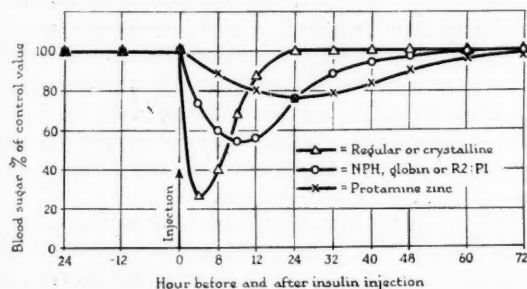


FIGURE 1 Average diagrammatic curves of response of blood sugar in human diabetics to single large subcutaneous injections of plain insulin (triangles), any of the commonly used intermediate insulins (circles) and protamine zinc insulin (crosses). Note that these three types of insulin bear a progressive and constant relationship to each other in four respects: 1) speed of action; 2) intensity of action at the peak; 3) time of peak action after injection; and 4) intensity of sustained effect. In these respects all insulins act differently in various individuals and in different dosages, but in the same dosage and individual their relation to each other is as shown.

In this category there are found individuals who have diabetes which is inherently mild but who are so insensitive to the action of insulin that they require it in fairly large amounts. In some chronic infections, congestive heart failure, certain patients with obesity and some endocrine disorders it is not unusual to find diabetes which requires 60 to 120 units of insulin daily, but which is easy to control with any type of depot insulin, even so. In these patients the differences in response to insulin and diet are purely quantitative, not qualitative. The diabetes is as mild, judged by all other criteria, as that of other patients in this class who require much smaller amounts of insulin.

Severe. The second category of severe diabetics who must use insulin routinely (Table 1) are more difficult to balance than the class just described. Yet they, too, can obtain good control and avoid insulin reactions, if proper methods are selected and employed.

Patients in this class usually are younger, thinner and have had diabetes longer than those with diabetes less

severe. Symptoms have been more prominent, weight loss more rapid and profound and acidosis more frequent. Insulin sensitivity is common, and reactions occur on less provocation. Blood and urine glucose levels are higher with less food intake.

The response of diabetes of this type to insulin is characteristic. It determines the choice of insulin preparations. When large amounts of any slow-acting insulin are used, heavy glycosuria is likely to follow meals even though hypoglycemia may occur during fasting, particularly in the night and before breakfast. Accordingly, when quick-acting insulins are used, high blood and urine sugar levels tend to appear before and after breakfast, and insulin reactions to occur during the day-time hours, especially at the time of peak action of the insulin used.

In diabetes thus characterized the use of one of the intermediate insulins is clearly indicated. In this country the ones which are available are globin insulin with zinc, NPH insulin, and thoroughly mixed combinations of plain and protamine insulin which contain two to three times as much plain as protamine insulin (2:1 to 3:1 mixtures).

The action of these modifications is quite similar in timing. In fairly large doses their peak action occurs in the middle of the 24 hours following their subcutaneous injection. The total action lasts at least 24 hours, thus providing substantial overlapping of effect when given once daily. The average behavior of a large single dose of any of them is illustrated diagrammatically in Figure 1. There is too little difference between them to exhibit them separately.

Acceleration and intensification of action is easily obtained by adding regular insulin to any of these intermediate preparations. Appreciable alteration is seen from plain insulin increments of at least 10 per cent with NPH insulin and 2:1 mixtures, and 50 per cent with globin insulin. These combinations are stable enough for practical purposes when prepared one ampoule at a time and kept cool. They must be mixed thoroughly, preferably in the ampoule.

As illustrated in Figure 1, these intermediate modifications are all quite different in action from regular or crystalline insulin at one extreme, and protamine zinc insulin at the other. Those are the standard quickly and slowly acting preparations, respectively, the first useful chiefly in emergencies and the last in mild diabetes.

Application of knowledge of timing of insulins is a fairly simple process. In milder forms of diabetes the differences do not matter much. Selection of insulin can

be made almost at random. Good control is easy to obtain, because homeostatic mechanisms "take up the slack" caused by an imperfect fit between the insulin action, food supply and exercise.

In more severe diabetes, however, an imperfect fit is shown by tendencies for glycosuria on one hand, or hypoglycemia on the other, to appear at characteristic times of day or night. When fractional urinalyses, blood sugar reports and symptoms or signs of hypoglycemia make any given pattern of behavior apparent, corrections and adjustments are easily made, either by changes in the total amounts of food and insulin taken, or by transfer of food or insulin from one part of the day to another. To illustrate, glycosuria following breakfast (associated with high *fasting* blood sugar levels, as a rule), together with a tendency to hypoglycemia in the late afternoon, can be adjusted by either or both of two shifts; (1) of carbohydrate from breakfast to mid-afternoon, or (2) the use of a longer-acting insulin. This food transfer moves it from a high to a low sugar period. The use of a longer acting insulin transfers effective action from afternoon to night-time. Again, glycosuria before or after the evening meal, together with a tendency to hypoglycemia during the night, can be adjusted either by transfer of food from noon or evening meals to bedtime, by use of an insulin with less prolonged and more intense effect, or both. The effect here is to transpose sugar from day to night, or of insulin from night to day, or both.

By maneuvers such as these many severe diabetics can obtain good control, thereby preventing complications and postponing greater severity of their diabetes.

Labile. The most severe form of human diabetes (Table 1) has been called "brittle," "labile," "volatile," "unstable" and "total" by various authors. It is the most difficult of all to manage, by far. Without insulin people with this kind of diabetes would not live; indeed, they did not live very long before insulin. It is their ability to live because of insulin which makes their number significant, creating increasingly important problems of treatment.

It is estimated that some 10 to 20 per cent of all patients using insulin have diabetes this severe. It is characteristic of them that they cannot be kept "sugar-free" without great danger of severe insulin shock, or other intolerable penalties of treatment. On that account all authorities accept and condone some glycosuria as the lesser of two evils. The accepted doctrine approves of as little glycosuria as compatible with relative freedom from insulin shock and absence of ketosis.

Practically all juvenile and young persons with diabetes join this group eventually. Older people are in the minority, but substantial numbers do appear, particularly if they are thin or if their diabetes has been present long. Chronic diseases, like active tuberculosis and hyperthyroidism, often make milder forms of diabetes this severe. Waves of heavy glycosuria with ketonuria, and of hypoglycemia with severe insulin shock, appear unpredictably and without evident causes. Severe acidosis occurs with great ease. Normal weight is not easy to maintain. Trauma, acute infection and anaesthesia are hazardous, not because of danger of gangrene or other vascular accidents, but because they may result in sharp increases in insulin requirement or severe acidosis. Routine insulin dosage is usually large, but not necessarily so, because many of the patients are children. Others are very sensitive to insulin, thus needing only relatively small amounts.

Glycosuria is often condoned in diabetes less severe than this, because poor control due to carelessness or ignorance is confused with the unavoidable poor control of labile diabetes. With proper application of insulin technics, however, some patients thought to be uncontrollable are found to be stable, and "maximum" grades of severity seen to improve.

Allowances of carbohydrate should be somewhat more generous in diabetes of this type than when it is milder. There are several reasons for this. Glucose lost in the urine should be replaced. Post-prandial glycosuria is often unavoidable. Extra carbohydrate feedings are desirable between meals to forestall reactions, especially during exercise. Children and young adults need more anti-ketogenic protection than old people. Nevertheless, the extravagance of an unrestricted carbohydrate intake causes unnecessarily heavy glycosuria, defeating its intended purpose and invoking the law of diminishing returns.

Unmodified insulin in frequent dosage is undoubtedly the most predictable insulin for treatment of diabetes this severe. An injection every six hours or so, with food, including one at midnight or later during normal sleeping hours, will provide the best possible control with least danger of reactions.* But the inconvenience of a frequent injection routine such as this makes it virtually intolerable. It was the chief cause of the need for, and development of, the depot insulins.

*This fact provides good proof of the fact that it is the unpredictable action of depot insulins, rather than unknown endogenous factors or irregular food supplies, which is responsible for the irregular behavior of diabetes of this variety.

A good compromise between accuracy and convenience in the treatment of diabetes as severe as this, is the use of a fairly quick-acting insulin modification twice daily. Any of the following is suitable: a mixture of three or four parts regular insulin to one part of protamine zinc insulin; globin or NPH insulin with regular insulin added to speed and intensify effect and increase predictability. From two-thirds to three-fourths of the insulin needed daily is given before breakfast and the balance at bedtime, along with a lunch. Interval feedings are given in the mid-morning and mid-afternoon; hence, regular meals are somewhat smaller, and glycosuria following them likely to be less in amount. The size of the morning dose is judged by the behavior in the late afternoon and evening; the night dose by that at breakfast time.

ACUTE COMPLICATIONS

Any of the varieties of diabetes may become complicated by acute illness, most commonly acute infections (especially those with fever), severe trauma, major surgery, general anaesthesia, congestive heart failure, and intense emotional stress. Frequent tests for sugar and ketones are mandatory, and their prompt control is essential to prevent the appearance of a vicious cycle which may prove fatal.

Many methods of emergency treatment have been devised. All depend on three important principles:

1. Reliance solely on unmodified insulin.
2. Frequent injection, at least every six hours night and day, to insure overlapping of effect.
3. Frequent testing to judge the effect of prior ad-

ministration and, therefore, the need for subsequent insulin.

In the interests of simplicity, a depot insulin previously used by any patient should be continued without change of dosage. For the same reason, one should not be started if not in routine use. Regulation with the most appropriate depot insulin should be resumed when the acute illness has subsided, good control has been secured, and the insulin requirement is neither changing rapidly nor excessive in amount.

SUMMARY

Almost all human diabetes mellitus is idiopathic in origin and requires continuous supportive therapy.

All grades of severity of diabetes are encountered in practice, from that which is barely detectable to that which is virtually total. This represents an increasing loss of automatic ability to utilize food normally, involves greater difficulty in maintaining normality, and requires increasing faithfulness and skill to secure the best possible control.

From the standpoint of supportive therapy, three major categories exist: (a) mild forms manageable by diet; (b) severe forms requiring various insulin technics; and (c) all forms complicated by acute illness which demands emergency measures.

By the intelligent use of food, insulin and certain adjunctive measures, normal nutrition and metabolic equilibrium can be maintained in the vast majority of diabetic subjects, with preservation of tolerance, prevention of complications, and protection of health.

The Challenge of Diabetes

What an opportunity for young doctors! Diabetes was twenty-seventh and is now eighth and almost inevitably soon to be sixth. Even if it is not the sixth cause of death, and that is quite possible because of statistical factors in reporting, at least it will rank sixth as the coincident disease. Diabetes is a disease for the doctor to follow throughout his whole medical career. It is so important for him from a financial and soul-satisfying standpoint that when he opens his office, his laboratory and his paraphernalia for treatment should be ready.

And if he can only secure one case his first year and treat that case well and at the same time protect the patient's family, he will not wait long before another glycosuric rings his bell. For that one case he can begin the compilation of his own diabetic manual, which he will give, already prepared, to his second case. Each doc-

tor advantageously can compose his own diabetic primer, resting assured that if he does not do this, patients will secure one written by another doctor. This is still a free country and there is freedom of the press and patients want to learn about their disease.

Tomorrow's Treatment. In the pituitary gland there is a hormone, not yet isolated, which injected into a dog will cause diabetes, but with each injection until the last massive dose there is a struggle for reversal of the process. There must be something like an anti-diabetic hormone. Which one of you will discover it?

From *Diabetes Yesterday, Today and Tomorrow* by Elliott P. Joslin, M.D., in *Proceedings of the American Diabetes Association*, Vol. 1, page 137, 1941.

The Management of Diabetes Mellitus in Children

A. L. Chute, M.D. TORONTO

The successful management of diabetes in children has been possible only since the discovery of insulin a little over thirty years ago. Prior to this, diets with extreme reduction of calories, especially those derived from carbohydrate, prolonged the lives of these children for a few weeks or months. The treatment was virtually starvation and few children survived more than two years.

As knowledge of the action of insulin increased, diets were liberalized both in calories and in the proportion of carbohydrate which they contained until it was shown that most diabetic children are readily controlled on a normal mixed diet for their age.

The chief problem in the management of the diabetic, however, is the loss of automatic control over insulin liberation. As has frequently been said, what is wanted clinically is an insulin that will be more active when the blood sugar is high and will be inactive or fail to be absorbed, when the blood sugar is low. Since this utopia is not in sight, the only means of regulating the glycemia of the diabetic is the proper distribution of the diet in relation to the time action of the insulin employed. This calls for considerable knowledge and experience on the part of the parent and the patient. Knowledge implies education.

EDUCATION OF PATIENT AND PARENTS

If properly undertaken, several hours on successive days should be spent teaching the parent and the child the preparation of diets and the need for insulin, its mode of administration and time of action. The signs of insulin overdosage and its remedy, the signs of acidosis,

urine testing and precautions to be taken during infection, must all be thoroughly understood before the patient leaves the hospital. This time spent on education is obligatory, if the application of the generally accepted principles of diabetic management are to have any meaning.

Without intelligent cooperation and understanding on the part of the parent and the child, elaborate calculation of diet, and the careful regulation of insulin, are at best a wasted effort—at their worst, a false cloak of security.

STANDARDS OF DIETARY TREATMENT

Recently, some groups in Scandinavia and latterly on this continent appear to have adopted the attitude that the diabetic cannot be taught or else has not the moral fibre to adhere to the rules of a diabetic regimen. Accordingly, they have advocated a more or less free diet on which the individual has nearly constant hyperglycemia and glycosuria. They claim that hyperglycemia and glycosuria have not been shown to be harmful so long as there is no excessive urinary output and sufficient insulin is taken to prevent ketosis. They emphasize the point that such management makes it possible for the child to lead a more normal social life, and is less likely to develop in him psychological disturbances. They also point to the fact that certain reports suggest that the incidence of severe complications are inevitable whatever type of diabetic management is employed and that efforts at careful control are therefore an unnecessary and unrewarding burden.

In a great many cases, if sufficient time is spent on educating the patient and the parent, and if each visit to the clinic or office is made the opportunity for further training, an intelligent and honest effort is made to follow the rules. This self-discipline shows in other phases of the patient's life and tends to develop character. This

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is especially true if in teaching diabetics emphasis is laid on the fact that control of diabetes means a chance to live—not that one lives to control diabetes. Some patients, it is true, do not measure up to such standards and are likely to follow the free regimen on their own initiative.

An increasing number of reports from various centers, indicate that there is a high incidence of vascular complications involving vital organs in long duration (over twenty years) juvenile diabetics. Many of these reports further indicate a fairly constant relation between the degree of diabetic control and the development of complications. For these reasons, a prescribed dietary regimen is considered advisable.

DIETARY REQUIREMENTS

The diet for a diabetic child must fulfill all the criteria for the diet of a normal child of the same age. It must be adequate in calories, minerals and vitamins, as well as in the essential elements of carbohydrate, fat and protein. The proportion of the latter in the diet should approximate those of any balanced nondiabetic diet.

In the Hospital for Sick Children, Toronto, we use the proportion of 2 grams of carbohydrate to 1 gm. of fat and 0.9 gm. of protein. Diets are most readily calculated according to age. We employ five main diets ranging from 1430 calories for the three to five year olds, to 2450 calories for the sixteen year olds. Sample menus are provided for each patient. These are planned to employ the usual fare provided for the rest of the family with the possible exception of the dessert. School lunch menus are provided for those who cannot come home at noon. These also prove useful in the summer as a basis for picnic lunches. To secure more nearly uniform blood sugar levels, six meals a day are customary. These consist of three main meals; breakfast, luncheon, dinner, and three small collations (containing 10 to 15 gm. of carbohydrate) at midmorning, midafternoon and bedtime. Diabetic control is greatly facilitated if the food is weighed. However, older children should be taught to gauge portions and understand how to make suitable substitutions in order that occasional meals may be taken out with friends, or in restaurants, without embarrassment or major loss of diabetic regulation.

The importance of catering to the individual taste of the child should be emphasized if cooperation on his part is to be expected. This can nearly always be achieved while remaining within the limits of the dietary prescription. In such matters, the assistance of a trained dietitian is invaluable. She can frequently satisfy hungry boys by increasing bulk with the addition of low car-

bohydrate vegetables and foods. Smaller children with less appetite may need to have the diet adjusted to contain more of the concentrated articles of diet, e.g. bread and cereals.

MODIFICATION OF THE DIET DURING ILLNESS OR CHANGE IN ACTIVITIES

In case of illness, of moderate severity, the total caloric intake is reduced to $2/3$ of the normal amount, but the usual foods may be consumed. In serious illness, a liquid diet is employed consisting chiefly of fruit juices and milk, equal to $2/3$ of the usual caloric requirement. At camp or when the child is taking part in athletic activities, an increase in the diet is necessary, 200—400 calories a day may be required in addition to their normal intake. Increasing the diet to the next highest age group is usually most satisfactory, since our diets are so arranged that there is approximately a 200 calorie difference between each diet. Under-nutrition must be avoided in the treatment of juvenile diabetes. It leads to rebellion and rejection of all control; or if strenuously imposed; is a factor in physical underdevelopment and may cause behaviour problems and psychological disturbances.

The use of diabetic ginger ale made with saccharin, and diabetic candies—which have no food value, while not recommended—are often helpful on certain occasions such as birthdays and at Christmas.

REGULATION OF INSULIN TREATMENT

Insulin is a necessity for all diabetic children. It should be employed as soon as the diagnosis is established and must never be omitted. The knowledge of the types of insulin, in regard to time of onset, maximum effect and duration is essential for intelligent use. Briefly, unmodified or regular insulin has an onset of action in one hour; its maximum effect is reached in four hours and its duration is eight hours. Protamine zinc insulin has a delay in its onset of action for approximately six hours. Its maximum effect occurs in 18-20 hours and the duration of action may be 36 hours or longer. Globin Insulin has an onset of action in two hours; a maximum effect in eight hours; a duration of action of approximately twenty hours. NPH insulin has an onset of action in two hours, a maximum effect in eight hours and a duration of action 24 hours. In our experience, the most satisfactory regimen in regard to insulin administration is to give both unmodified insulin and protamine zinc insulin in separate injections approximately twenty minutes before breakfast. In general $2/3$ of the total dose is given as protamine zinc insulin and $1/3$ as unmodified insulin.

In younger children under the age of five, it is found that larger amounts of unmodified insulin are required and equal amounts of each type of insulin appear to give better results.

Recently, NPH Insulin, a new form of protamine insulin, has been used. It seemed to have a special advantage in the fact that a single daily injection would control many cases, or if unmodified insulin were required as well, it could be mixed with the NPH without significant change in the action of either insulin.

However, after two years experience with this insulin which seems to give good control initially in many cases, we have been forced to revert to the use of protamine zinc insulin and regular insulin as separate injections in most cases. This has been due to severe and unpredictable reactions which have been coupled with marked morning hyperglycemia.

INDIVIDUAL ADJUSTMENTS OF THERAPY

It should be emphasized that each patient requires individual study to determine the best insulin regimen and the most suitable dietary distribution to bring about satisfactory regulation of his diabetic state. Rapid fluctuations from glycosuria to insulin reactions are frequent occurrence in children, because diabetes is more labile in the young. In addition, variations in exercise and the frequency of infections upset the normal balance. To maintain reasonable control, the urine must be tested frequently—before each meal and at bedtime are ideal. However, in practice, a test before breakfast and one at 4 p.m. are useful guides. The morning test indicates whether the long-acting protamine zinc insulin is adequate, while the 4 p.m. test indicates whether enough of the quick-acting unmodified insulin is being employed. Patients are taught to ignore occasional glycosuria; but glycosuria persisting for more than two to three days requires an increase in the insulin dosage. On the other hand, reactions occurring before lunch indicate an excess of unmodified insulin while nocturnal or early morning reactions are attributable to protamine zinc insulin. Such reactions require the reduction of the appropriate insulin. Reactions from the long acting insulin such as protamine and NPH are less distinct than those due to unmodified insulin and are often manifest simply as drowsiness or inability to concentrate. Children who do poorly in early morning classes but are brighter later in the day probably need the dose of protamine zinc insulin decreased. A fast-

ing blood sugar test should settle this problem. Mild reactions can be controlled with a teaspoonful of corn syrup, two lumps of sugar, or a piece of candy. If the child is unconscious, the parents are instructed to give nothing by mouth, and to inject a $\frac{1}{4}$ to $\frac{1}{2}$ cc. of epinephrine hydrochloride intramuscularly; if this is not effective a physician should inject 25 to 50 ccs. of 50 per cent glucose intravenously.

EXERCISE

Exercise plays a prominent part in the control of diabetes in children. Carbohydrate is burned with a greater economy of insulin during activity than at rest. Unaccustomed exercise by a diabetic patient receiving adequate insulin therefore may lead to an insulin reaction. In uncontrolled diabetes, on the other hand, exercise may cause increased fat utilization which in turn leads to ketosis and may lead to acidosis and possibly coma.

MENTAL HYGIENE

The psychological management of diabetic children is immensely important. Summer camps are an excellent aid in solving many of their problems. Over-dependent children can be made more self-reliant and, by example from other children, learn to give their own insulin. They learn that they can live an active outdoor life like fishing or swimming without loss of diabetic control.

For the juvenile diabetic, especially, the development of a balanced outlook toward life and his disease requires the sympathetic understanding of the parent and the constant guidance and encouragement of the physician. The physician who takes the time and effort to deal with the many human problems as well as the technical management of juvenile diabetes, will find himself amply repaid by the gratitude of his patients.

CONCLUSION

In summary, the management of a juvenile diabetic revolves about four major principles—insulin administration, dietary regulation, control of exercise and adequate education of patient and parent.

Diabetic control which approximates as closely as possible the normal physiological state is the only means apparent to reduce the incidence of the late complications (coronary disease, retinopathy and neuropathy) of juvenile diabetes.

Dietary Instruction for the Diabetic

Deaconess Maude Behrman, M.S. PHILADELPHIA

The diet for the diabetic, if properly planned, can be both nutritious and satisfying. If it is calculated to fit the patient's needs there should be no difficulty in following it. The day is gone when the patient was given a diet list and told to follow the menu printed on it for the rest of his life. He needs instruction and can be taught simply and effectively how to follow the diet.

THE INDIVIDUAL DIETARY PRESCRIPTION

Every diabetic needs to know and understand why his diet has been planned especially for him. The diet which has been given to his neighbor who is also a diabetic may not be suitable for him. The caloric value, for example, should meet the needs of the individual according to his desirable weight and activity. Since it is better for the diabetic to be slightly below average weight, the caloric value of the prescribed diet is usually slightly lower than that of the nondiabetic. On the other hand, if the diabetic is markedly below desirable weight, his diet should contain sufficient calories to allow him to gain weight.

In the "Diabetes Guide Book for the Physician" of the American Diabetes Association are six sample diets which range in caloric value from 1200 to 2600. The carbohydrate content varies from 125 gm. to 250 gm., the protein from 60 to 100 gm. and the fat from 50 to 130 gm. These sample diets can satisfy the needs for many patients and can be readily modified to meet individual requirements to a close degree.

After the physician has planned the diet prescription in grams of carbohydrate, protein and fat to meet the

patient's needs, the diet must be calculated in terms of actual foods for the day. This must be carefully explained to the patient so that meal planning will be easy.

PERSONAL PREFERENCES AND FOOD HABITS OF THE PATIENT

In the past, diets for diabetics were often complicated and were given to the patient with little explanation. When emphasis was placed on weighing foods, this sometimes made the diabetic appear different from others. Diets were difficult to follow, and as a result, were not adhered to.

The diabetic must be thought of as a person living in an environment which may affect appreciably his ability to follow instructions. He will, no doubt, have definite food preferences. His economic status will influence the type of food he can purchase. He will also be faced with some emotional problems. Consider what goes on in a person's mind when he first learns that he has diabetes and must remain on a diet, perhaps for the rest of his life. For a time, the bottom seems to have dropped out of everything. The whole situation involves knowing many things about the patient and his home life.

Answers to such questions as the following should be obtained from the patient preparatory to dietary instruction: Where are meals eaten? Do lunches have to be packed and carried to work or school? Who prepares the meals? What facilities are available for the preparation and storage of food as a stove, broiler and refrigerator? Teaching a diet is not as easy as it sounds. Cooperation of the patient will be obtained only if he is closely involved in the planning of it.

It is also important to recognize that the patient usually has a certain amount of intellectual curiosity. In the past we have acted as though we knew something which was very mysterious and as if no one but a doctor or a dietitian would ever understand the cal-

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ulation of the diet. However, this is no longer necessary. I think we should give the patient an opportunity to learn all about food values. In this respect a diabetic has a real opportunity to learn something his nondiabetic friends will seldom take the time to learn. Some new diabetic diet material has recently been developed which greatly simplifies the teaching of the patient and which can be readily adjusted to the food habits of the individual²

THE ADA DIETS

This excellent dietary scheme developed by a joint committee of the American Diabetes Association, the American Dietetic Association, and the Diabetes Section of the Public Health Service is described in the "Diabetes Guide Book for the Physician."¹ This material is being widely used.

Caso² has summarized the work of this joint committee and explained some of the difficulties that were encountered in developing this diet material. There is a great variation in the composition of foods due to varietal differences, variations in conditions of growth, degree of maturity, and the methods of harvesting, storage or preparation. In addition to the food variables, there is also a great variation from "day-to-day in bodily requirements and utilization of food which is dependent on such factors as activity, emotional status and insulin dosage." It was pointed out "that differences in bodily needs far exceed differences in food composition and therefore minimize the problem of the inevitable variation in food content." The important conclusion which was reached by this joint committee was that only a reasonable amount of detail is justified in calculating diabetic diets.

FOOD EXCHANGE LISTS

The common foods of similar composition were grouped in six lists in quantities which have approximately equivalent food value. The average food values for each group are given in Table 1.

Table 2 contains the six exchange lists which include most of the common foods which the diabetic may eat.

TABLE 1. Composition of Food Exchanges

List	Food	Measures	Gm.	C	P	F	Cal.
1	Milk Exchange	1/2 pint	240	12	8	10	170
2a	Vegetable Exchanges	as desired	—	—	—	—	—
2b	Vegetable Exchanges	1/2 cup	100	7	2	—	36
3	Fruit Exchanges	varies	—	10	—	—	40
4	Bread Exchanges	varies	—	15	2	—	68
5	Meat Exchanges	1 oz.	30	—	7	5	73
6	Fat Exchanges	1 tsp.	5	—	—	5	45

TABLE 2. The Six Exchange Lists

LIST 1. MILK EXCHANGES

Carb.—12gm., Protein—8 gm., Fat—10 gm., Calories 170

	Meas.	Gm.
* Milk, whole	1 cup	240
Milk, evaporated	1/2 cup	120
* Milk, powdered	1/4 cup	35
* Buttermilk	1 cup	240
* Add 2 fat exchanges if fat free		

LIST 2. VEGETABLE EXCHANGES

A.—These vegetables may be used as desired in ordinary amounts. Carbohydrate and Calories negligible.

Asparagus	"Greens"	Lettuce
Broccoli	Beet	Mushrooms
Brussels Sprouts	Chard	Okra
Cabbage	Collard	Pepper
Cauliflower	Dandelion	Radishes
Celery	Kale	Rhubarb
Chicory	Mustard	Sauerkraut
Cucumbers	Spinach	String Beans,
Escarole	Turnip	young
Eggplant		Summer Squash
		Tomatoes

B.—Vegetables: 1 Serving equals 1/2 cup equals 100 grams
Carb.—7 gm., Protein—2 gm., Calories—36

Beets	Peas, green	Squash, winter
Carrots	Pumpkin	Turnip
Onions	Rutabaga	

LIST 3. FRUIT EXCHANGES

Carbohydrate—10 gm., Calories—40

	Meas.	Gm.
Apple	1 sm. (2" diam.)	80
Applesauce	1/2 cup	100
Apricots, fresh	2 medium	100
Apricots, dried	4 halves	20
Banana	1/2 small	50
Berries: Straw., Rasp., Black	1 cup	150
Blueberries	2/3 cup	100
Cantaloupe	1/4 (6" diam.)	200
Cherries	10 large or 15 small	75
Dates	2	15
Figs, fresh	2 large	50
Figs, dried	1 small	15
Grapefruit	1/2 small	125
Grapefruit Juice	1/2 cup	100
Grapes	12	75
Grape Juice	1/4 cup	60
Honeydew Melon	1/8 (7" diam.)	150
Mango	1/2 small	70
Orange	1 small	100
Orange Juice	1/2 cup	100
Papaya	1/3 medium	100
Peach	1 medium	100
Pear	1 small	100
Pineapple	1/2 cup	80
Pineapple Juice	1/3 cup	80
Plums	2 medium	100
Prunes, dried	2 medium	25
Raisins	2 Tbsp. level	15
Tangerine	1 large	100
Watermelon	1 cup	175

LIST 4. BREAD EXCHANGES

Carbohydrate—15 gm., Protein—2 gm., Calories—68

	Meas.	Gm.
Bread	1 slice	25
Biscuit, Roll	1 (2" diam.)	35
Muffin	1 (2" diam.)	35
Cornbread	1 (1½" cube)	35
Flour	2½ Tbsp.	20
Cereal, cooked	½ cup	100
Cereal, dry (flake & puffed)	¾ cup	20
Rice, Grits, cooked	½ cup	100
Spaghetti, Noodles, etc., cooked	½ cup	100
Crackers, graham (2½" sq.)	2	20
Oyster	20 (½ cup)	20
Saltines (2" sq.)	5	20
Soda (2½" sq.)	3	20
Round, thin (1½" diam.)	6-8	20
Vegetables		
Beans & Peas, dried, cooked	½ cup	90
(lima, navy, split pea, cowpeas, etc.)		
Baked Beans, no pork	¼ cup	50
Corn	⅓ cup	80
Parsnips	⅔ cup	125
Potatoes, white, baked, boiled	1 (2" diam.)	100
Potatoes, white, mashed	½ cup	100
Potatoes, sweet, or Yams	¼ cup	50
Sponge Cake, plain	1 (1½" cube)	25
Ice Cream (Omit 2 fat exchanges) ..	½ cup	70

LIST 5. MEAT EXCHANGES

Protein—7 gm., Fat—5 gm., Calories—73

	Meas.	Gm.
Meat & Poultry (med. fat)	1 oz.	30
(beef, lamb, pork, liver, chicken, etc.)		
Cold Cuts (4½" sq., ⅛" thick)	1 slice	45
Frankfurter	1 (8-9 lb.)	50
Fish: Cod, Mackerel, etc.	1 oz.	30
Salmon, Tuna, Crab	¼ cup	30
Oysters, Shrimp, Clams	5 small	45
Sardines	3 medium	30
Cheese, cheddar, American	1 oz.	30
Cottage	¼ cup	45
Egg	1	50
Peanut Butter*	2 Tbsp.	30

* Limit use or adjust carbohydrate.

LIST 6. FAT EXCHANGES

Fat—5 gm., Calories—45

	Meas.	Gm.
Butter or Margarine	1 tsp.	5
Bacon, crisp	1 slice	10
Cream, light, 20%	2 Tbsp.	30
Cream, heavy, 40%	1 Tbsp.	15
Cream Cheese	1 Tbsp.	15
French Dressing	1 Tbsp.	15
Mayonnaise	1 tsp.	5
Oil or Cooking Fat	1 tsp.	5
Nuts	6 small	10
Olives	5 small	50
Avocado	⅓ (4" diam.)	25

List 1 includes milk in its different forms. The unit of measure is ½ pint (one measuring cup) of whole milk. In most parts of the country this unit is a common size serving.

The newer knowledge of the sugar content of fruits and vegetables, as described by Olmsted³, was used in preparation of the vegetable and fruit exchange lists. Vegetables are listed in 2 groups, A and B. The A vegetables are those so low in carbohydrate and calories that they can be used practically as desired, providing the amount of those served cooked does not exceed one cup daily. Usually only ½ cup or 100 gm. of a B vegetable is included in the daily food allowance; there are only a few to choose from and more variety may be obtained from the A list.

The fruit list shows portions or servings, representing 10 gm. of carbohydrate. Usually 3 to 5 servings are allowed daily. The patient is shown how he may choose any fruit from the list, provided he take a portion of the designated size.

The bread list includes foods which may be substituted for one slice of bread (weighing 25 gm.) The food in this list contains approximately 15 gm. of carbohydrate and 2 gm. of protein. In a diet of 1800 calories, for example, 8 or more bread exchanges may be included to provide the amount of carbohydrate prescribed in the diet. The patient does not actually have to eat the 8 or more slices of bread but may exchange some of them for such things as ½ cup of potato or ¾ cup of dry cereal.

In the meat exchange list, the unit is one ounce of meat, representing 7 gm. of protein and 5 gm. of fat. If the patient is given three meat exchanges for a day he may take three different foods in the amount designated or three exchanges of one food.

In the list of foods rich in fat, one fat exchange is represented by such things as one level teaspoon of butter, a strip of bacon or 2 tablespoons of light cream.

PREPARATION OF THE MEAL PLAN

Each patient is allowed a specific number of items from each of the exchange lists on the basis of the amount of carbohydrate, protein and fat prescribed. To calculate the diet prescription, a patient must have on hand, or be acquainted with composition of the food groups. (Table 1) This does not involve many figures and after calculating a few diets, one finds that the figures remain in the memory. In Table 3 is shown the number of exchanges from each of the six lists required to fill a diet prescription for carbohydrate—150 gm., protein—70 gm., fat—70 gm., calories—1500.

TABLE 3. Sample Diabetic Diet. Food for the Day

Food	List Exchange	Amount	Carbo- hydrate	Protein	Fat
Milk	1.	1 pint	24	16	20
Vegetable A	2.	Any amount	—	—	—
Vegetable B	2.	1 serving	7	2	—
Fruit	3.	3 servings	30	—	—
Bread Exchanges	4.	6	90	12	—
Meat Exchanges	5.	6	—	42	30
Fat Exchanges	6.	4	—	—	20
Total			151	72	70

The next step involves dividing the total day's food into 3 or 4 meals as the physician desires. (Table 4)

TABLE 4. Sample Meal Plan**Breakfast:**

- 1 Fruit Exchange from List 3
- 1 Meat Exchange from List 5
- 1 Bread Exchange from List 4
- 1 Fat Exchange from List 6
- Coffee or Tea (any amount)

Lunch or Supper:

- 2 Meat Exchanges from List 5
- 2 Bread Exchanges from List 4
- Vegetable from List 2A (any amount)
- 1 Fruit Exchange from List 3
- 1 cup Milk from List 1*
- 1 Fat Exchange from List 6
- Coffee or Tea (any amount)

Dinner or Main Meal:

- 3 Meat Exchanges from List 5
- 2 Bread Exchanges from List 4
- Vegetable from List 2A (any amount)
- 1 Vegetable Exchange from List 2B
- 1 Fruit Exchange from List 3
- 1 Fat Exchange from List 6
- Coffee or Tea (any amount)

Bedtime:

- 1 cup Milk from List 1*
- 1 Bread Exchange from List 4
- 1 Fat Exchange from List 6

*Part of milk may be used for coffee, tea or for cereal

From this meal plan, many varieties of menus may be planned. It may be used as a guide in selecting the food from the regular menu of the family. Eating out is very simple. Keeping the meal plan in mind one uses the restaurant menu and makes selections of plain food which are exchanges of the above.

In this manner many menus can be planned, and combinations of foods made into many varied recipes. Diabetics can be taught to make their own recipes. An example of how this is done may be given to the patient. If the diet calls for a bread exchange, a meat exchange and 1 cup of milk, he can be told that the bread may be exchanged for 1/2 cup of macaroni, the meat exchanged for 1 ounce of cheese and using one half the allowed portion of milk, these can be

combined as is any recipe for macaroni and cheese.

A few additional suggestions need to be given to the diabetic concerning the use of "special diabetic foods." There is no need for these and in fact there is no place for these in the management of the modern diet for the diabetic. Emphasis should be placed on trying to eliminate the desire for sweet foods and the use of artificial sweeteners in place of sugar.

SAMPLE MENUS BASED ON ABOVE DIET

MENU No. 1**Breakfast:**

- 1/2 cup orange juice
- 1 soft cooked egg
- 1 slice whole-grain bread, toasted
- 1 teaspoon butter
- Coffee

Lunch:

(Packed lunch—carried to work or school)

- (Lettuce leaf
- 1 slice bologna
- 1 slice cheese
- 2 slices bread
- 1 teaspoon butter
- 1 small apple
- 1/2 pint of milk

Dinner:

- 1/2 cup tomato juice
- 3 ounces roast beef
- 1/2 cup peas
- 1/2 cup noodles
- 1 slice bread—1 teaspoon butter
- 1/2 grapefruit, broiled
- Tea or coffee

Bedtime:

- 1 cup milk
- 5 saltines
- 1 teaspoon butter

MENU No. 2**Breakfast:**

- 1/2 cup apple sauce
- 1 poached egg on 1 slice toast with 1 teaspoon butter
- Coffee

Lunch:

- Rice soup (made from broth and 1/2 cup rice)
- Egg, hard cooked (1) and 5 shrimp on lettuce with tomato wedges and parsley
- 1 teaspoon mayonnaise
- 1 (1 oz.) roll
- 1 cup strawberries
- 1 cup milk

Dinner:

- 1/2 cup carrots
- 3 ounces steamed halibut
- 1 small baked potato
- 2 celery sticks
- 1 slice bread—1 teaspoon butter
- 1 medium sliced fresh pear
- Tea or coffee

Bedtime:

- 1 cup milk
- 2 graham crackers
- 1 tablespoon cream cheese

MENU No. 3

Breakfast:

1/2 grapefruit
1 egg fried in 1 teaspoon of allowed butter
1 slice bread
Coffee

Lunch:

1/2 cup tomato juice (hot)
Toasted cheese sandwich (2 slices cheese, 2 slices of bread and 1 strip of bacon)
2 halves peaches (cooked with no added sugar)
1 cup milk

Dinner:

1 large pork chop (3 ounces)
1/2 cup mashed potato
Lettuce hearts with vinegar
1/2 cup beets
1 small roll—1 teaspoon butter
1 medium apple baked with cinnamon
Tea or coffee

Bedtime:

1 cup milk
1 slice toast
1 teaspoon butter

SUMMARY

The scheme of diet planning contained in the "Diabetes Guide Book for the Physician" published by

The American Diabetes Association has proved simple and effective. Experiences with the exchanges has proved to us that the patient learns to understand the diet and in turn follows the diet with interest. The doctor is not burdened with needless detail in figuring and interpreting the diet to the patient, and the dietitian is most happy of all because of the cooperation of the patient and the doctor. A healthy diabetic under good control is the gratifying result of well balanced meals including all the essentials recommended for the normal diet.

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Acceptance of the ADA Diets and Exchange Lists

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For the first time in this country, a nationwide effort has been made towards simplifying and unifying a form of dietary treatment. This pioneer step has been taken in the field of diabetic diets. To accomplish this a committee consisting of representatives of the American Diabetes Association, the American Dietetic Association and the Diabetes Section, Public Health Service worked together over a period of three years. The results of their efforts are as follows:¹⁻² 1) A short

table of food values for calculating the composition of diabetic diets. 2) A set of six exchange lists which contain foods of similar composition and which may therefore be substituted for one another. 3) An easy method for calculating diabetic diets based on these food values and exchange lists. 4) Six sample diets* at different caloric levels and with varying amounts of carbohydrate, protein and fat. 5) An illustrated diet booklet "Meal Planning with Exchange Lists"³ for the physician to give to the patient.

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*In preference to a term like "New Diets" or "Standard Diets" it was decided to use the term "ADA Diets." Although all on the joint committees were members of one or the other of the ADA's concerned, the important contribution of the staff of the Diabetes Section of the U.S. Public Health Service should not be overlooked. Ed.

There were several reasons which prompted this joint effort: 1) Need for a diet plan which would assure a nutritionally adequate diet for the person with diabetes. 2) Need for consistency in the inclusion or exclusion of common foods in the diabetic diet. 3) Need for servings of foods to be expressed in practical amounts which would be easy to measure. 4) Need for diet material which would be easy to use in instructing the patient and which would be flexible so that it could be adjusted to individual food habits.

The results of this project are most gratifying. It is being widely accepted. The diet material appears in several recent textbooks.³⁻⁸ Without undertaking a widespread survey it is impossible to determine how many hospitals and physicians are using this new diet material. However, there are records of approximately 1000 hospitals and 1200 physicians in the country who have adopted this method of planning diabetic diets. This latter figure is undoubtedly a conservative one. The use of this new diabetic diet material by a hospital usually implies that it has first been accepted by the medical staff of the institution. Therefore, it is more likely that there are at least 2000 physicians familiar with the material and using it in their practice.

WIDELY AVAILABLE

The use of this material has not been centered in a few areas of the country. Reports show that hospitals and physicians in every state have adopted these diets. New York, Pennsylvania, Massachusetts, Connecticut, Florida, Ohio, Wisconsin, Kansas, Texas and California are the states which appear to rank the highest in general use of these diets. It is interesting to note that Spanish translations have been made for use in Puerto Rico, Mexico and the South American countries. It has also spread into Canada.

In the past it was not uncommon for several hospitals in a city to have different methods of planning diabetic diets. In several cities the majority of institutions are now using this new method. This uniformity naturally makes it much easier for the professional staff.

Colleges and universities over the country are instructing medical students, nurses, and dietitians in the new diabetic diet material. Several visiting nurse asso-

ciations, upon request of local physicians, are engaged in patient education and have adopted the new Meal Planning booklet⁹ as the basis of dietary instruction. State and local health departments have also obtained copies of the booklet, which are being used mostly by the public health nurse or nutritionist who has introduced it to local physicians, small hospitals, and nursing homes.

Professional workers have also been pleased with this standardization of diabetic diets. Student nurses, medical and dietetic internes affiliating with different hospitals, find it much easier now that the same procedure for planning diabetic diets is used in many different institutions.

Persons with diabetes have reacted most favorably to this diet material. Patients can now discuss their diets with other diabetics in their community and have some common ground of understanding. In the past it was not uncommon for diabetics to be exposed to three or four different diet systems if they moved from one community to another. In fact, different members of the same household who were diabetics might have markedly different diet plans if they obtained medical care from different sources.

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Social Aspects of Diabetes Mellitus

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In addition to the longer life span, which is now the logical expectation of the diabetic, the incidence of the disease itself continues to increase. It is estimated that there are at present, in this country alone, about 250,000 diabetics whose existence is known, not to speak of those who are as yet undiscovered. It is not outside the bounds of possibility that within the next ten to fifteen years the number of known diabetics in the United Kingdom will reach the half-million mark. This growing army will inevitably create problems peculiar to itself which will color the picture of the national economy as a whole.

To illustrate this we have analyzed the records of 490 patients who have been referred to our department since January, 1947. Of this number 361 were true diabetics; 127 (35 per cent) were males, and 234 (65 per cent) were females. The ages of these patients ranged from five to 88 years and they were drawn from the ranks of almost every trade and profession. The Table shows the numbers for each year, and indicates the general trend of disease in a thickly-populated area which includes urban and rural districts.

TABLE 1 Increasing Incidence of Diabetes			
Year	Males	Females	Totals
1947	14	32	46
1948	26	33	59
1949	22	49	71
1950	17	47	64
1951	39	61	100
1952 (Jan.-Feb.)	9	12	21

Bearing these facts in mind, the authors felt that the social aspects of diabetes mellitus were worthy of careful study and critical review. The subject was fully discussed in a series of papers eighteen years ago by Joslin and his associates¹ (1934). In this country Lawrence and Madders² (1938) reported details of 100 employed

diabetics attending the Diabetic Department at King's College Hospital. More recently, other American workers (Beardwood,³ 1950; Dublin and Marks,⁴ 1950; Murray,⁵ 1950; Root,⁶ 1950) have published the results of their studies in relation to industry, health and employment. We propose in this paper to consider a number of important aspects of the disease as it affects the social and economic life of the patient and his family.

PRESENT STATUS OF DIABETIC CONTROL

Clinics for the treatment of diabetics are to be found in all parts of the country. The internal organization varies from one to another, depending largely on the personal views of the physician in charge; but all have a common basis on well established principles of dietary control, supplemented by insulin as and when required. Patients are referred to the clinic because of one symptom or another, by general practitioners and other hospital departments. A certain proportion are treated as outpatients and receive instructions regarding diet and the use of insulin. A large number, however, are admitted to either a general or diabetic ward for stabilization, and remain in the hospital for a varying period of weeks. This results in the occupation of much needed hospital beds, and in temporary loss of wage-earning capacity which has its repercussions on the patient's family. When one recalls the increasing incidence of diabetes it will be seen that the continuation of this system must, sooner or later, lead to a difficult situation. We ourselves are strongly opposed to the practice of admitting patients to a hospital for standardization, except in cases of pre-coma or where the severity of the diabetic condition is due to an aggravating factor such as gangrene, intercurrent infection, cardiac or renal failure, pulmonary tuberculosis etc. Our aim has been not only to keep the patient well, but also to prevent, as far as humanly possible, loss of working hours with consequent domestic upsets. Our methods of treatment and standardization have been described in a previous paper (Grunberg and Roberts,⁷ 1948) in which the importance of the social side was also stressed.

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DIABETES IN CHILDHOOD

Fortunately, diabetes mellitus is rare under the age of five. The difficulties in treatment are numerous; the liability to intercurrent disease, the changing requirements of growth, and the unpredictable outbursts of physical energy and emotional disturbance must all be taken into account by the physician in order to achieve satisfactory standardization. At home the diabetic child is, unfortunately, often given so much parental attention that other members of the family may feel themselves of secondary importance. This has its ill effects on the young patient himself for he becomes a dominant figure in the domestic scene and may take full advantage of the situation to gain his own ends.

Fresh obstacles arise as the child grows up and goes to school. Here he meets other children whose lives are not disturbed by dietary restrictions. He is overshadowed by a guilty secret and may go to great lengths to prevent his acquaintances learning of it. Parents are not always free from blame in this respect. As Fischer⁸ (1947) pointed out in a discussion of the emotional factors in diabetic children, "... frankness and understanding on the part of the family, as well as the patient, are absolutely essential if the child is to make a good social adjustment." The psychological aspect of diabetes in childhood and adolescence is of prime importance, and it plays an integral part at all ages; the majority, especially the younger ones, have a well marked "diabetic mentality" which often necessitates much patience and perseverance on the part of doctors and parents before it is overcome.

DIABETES IN THE YOUNG ADULT

During adolescence and in the period after leaving school, the problem of a career has to be seriously considered. In bygone years, the diabetic was automatically barred from certain occupations if his disability became known. Posts entailing long hours of work, with irregular meals and fluctuating energy requirements, were not for him; jobs which involved bearing responsibility for the safety of others were beyond his reach. In some cases difficulties during earlier years had led to imperfect or incomplete education, and the resulting gaps precluded the possibility of his entering the ranks of the "black-coated workers" or the professions. If he did obtain permanent employment, an unforeseen complication might put an end to it for a time at least. Some employers were not disposed to have diabetics on their staff because they looked on them as disabled persons and feared that they might not be able to do a normal day's work.

Another problem confronting the diabetic during these years is the question of marriage. The points at issue are usually one or more of the following: 1) Should I tell my prospective partner that I am a diabetic? 2) Should I have children? 3) If I do, are they likely to inherit diabetes? These are matters of great moment, and in dealing with them the physician must exercise understanding and tact.

DIABETES IN THE ELDERLY

As our patient approaches middle life and passes into his fifth decade, he becomes a likely candidate for those ailments to which all of us are prone.

The social implications of these conditions become evident when we remember the increasing number of diabetics who will ultimately enter the "arterio-sclerotic zone". No longer able to support themselves, they become an additional anxiety to their families; and those of them—and they are not few—who have no relatives or friends to whom they can turn, become the responsibility of the state. If they are ill enough to require hospital treatment they make additional demands upon an already understaffed and overworked hospital service; it is a matter of common knowledge how much tact and sympathy is needed in nursing old people—mere technical nursing and medical skill is not enough. For those who are not in need of hospital care, arrangements must be made for their domestic well-being; their homes must be kept in order, their daily wants attended to, and even their injections of insulin may have to be given by the district nurse or by a friend. Thus it can be seen how, as the life span of the diabetic lengthens, his problems become to a greater extent those of the community as a whole.

THE INCREASING INCIDENCE OF DIABETES

The total number of known diabetics in this country alone has increased considerably in the last fifteen years. This is the result of several factors: 1) People live longer nowadays; mortality rates from acute illnesses such as pneumonia and other infections have been considerably reduced by the use of chemotherapy and antibiotics, and preventive measures against the communicable diseases have permitted more and more children to reach adult life. 2) Doctors realize the importance of routine urine testing in patients irrespective of the particular system affected. 3) The general public is more medically conscious, due in the main to the increasing prominence given in the lay press to medical subjects. Consequently, those who are hereditarily predisposed to diabetes are likely to reach middle

life, when obesity, with its tendency to precipitate diabetes, begins to make its appearance.

The conclusion to be drawn from the foregoing discussion is that diabetes mellitus is to be looked upon as a disease with widespread reactions on the community and on the state. The activities of the American Diabetes Association bring into focus the importance of a nationwide, if not a worldwide, campaign for the detection of diabetics. If we turn a blind eye to these unknown people, we shall be storing up a source of future ill health and disease which may well heavily tax the medical and social resources of the nation. Our experience over a number of years with a large diabetic community in this country has made it clear that, in view of the increasing numbers, the current approach to the diabetic problem is not adequate. We shall now put forward some suggestions which, in our opinion, would considerably benefit the life and outlook of the diabetic. Contributions towards the deeper understanding of diabetes have come from clinic and laboratory workers all over the world and, if the best possible use is to be made of new methods and fresh lines of research, there must be full international cooperation. With the recent establishment of the International Diabetes Federation, it is hoped to achieve such collaboration. In each country there should be a National Diabetes Association to act in an advisory capacity and represent the interests of the diabetic community.

As far as the individual diabetic clinic is concerned, its responsibility does not end with the assessment of the diabetic state, the prescription of diet and insulin and the provision of a chiropody service. It must also help the patient in his social difficulties.

Much is already being done for the children, in cases where home conditions are unsuitable, or where parents find themselves unable to cope with the general management of the patient. An all-important part of the initial treatment is to gain their confidence, and to form an idea of their mental attitude towards their condition. Where the physician feels that they would derive benefit from a period of special care, arrangements can be made for their admission into one of several homes which are already in existence. Here they are not only taught the principles of diet and how to give their own insulin injections, but also receive a good general education in order to prepare the way for employment when they reach adult life.

For the adult person, unable to obtain or keep a suitable job, we have found that personal contact with the employer and proper explanation of the diabetic

state eliminates the prejudice towards such people. In almost every case the diabetic himself, keen to hold his post and seldom absent due to illness because of regular medical supervision, has been an excellent advertisement for his fellow sufferers. The hospital almoner can be of the greatest assistance to the physician in the matter of finding employment.

We feel sure that most physicians in charge of diabetic clinics encounter, from time to time, elderly patients who are unable to care for themselves and who have no one to look after them. These people are frequently hampered by defective vision or hearing or are suffering from one or another of the vascular complications of the disease. Even though the almoner may in some cases be able to arrange home help, and though injections of insulin can be given by the district nurse or a relative, there remain others for whom this is insufficient. Realizing this, the Diabetic Association is establishing a home for such people at Kingston-on-Thames in Surrey but, of course, this will serve only a comparatively small area. The only solution would seem to be the setting up of similar establishments in other parts of the country so that these people would be assured of comfort and attention in their declining years.

SUMMARY

We have attempted in this paper to review the social and economic aspects of diabetes mellitus, basing our discussion on firsthand experience in dealing with a large number of diabetics of all ages and representing all trades and professions. Attention has been drawn to various problems which may arise during the diabetic life, and we have suggested methods by which some of these problems might be solved.

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Group Therapy of Obese Diabetic Patients

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The reported incidence of obesity in diabetes mellitus in the United States ranges from 57.8 per cent¹ to 90 per cent or more of all patients.²⁻⁸ The prevalence of obesity in this condition, added to the fact that the disease can be induced in animals by hyperalimentation, has led some authors to consider obesity an important etiologic factor in diabetes.⁹

Although there is no general agreement as to the criteria of good diabetic control it cannot be denied that the obese, middle-aged diabetic frequently becomes free from glycosuria or hyperglycemia after dietary restriction and weight loss. Sometimes the change seems tantamount to a cure;^{2, 3; 11-13} all evidence of diabetes disappears and the laboratory findings remain normal as long as the ideal weight is maintained. Duncan has emphasized the important point that weight reduction by means of a low caloric intake is "the most satisfactorily effective manner of controlling the diabetes." It can be said in fact that overweight diabetic patients who reduce weight by caloric restriction show consistently good results, whereas those who fail to reduce show extremely poor results, with or without insulin. Even diabetics of normal weight show improvement in regard to the diabetes following loss of weight. Consequently, in obesity associated with diabetes, a low caloric diet is indicated even more than in obesity of nondiabetic patients.

The benefit of weight reduction in diabetes mellitus was the underlying basis of the important principle of undernutrition established by Allen in 1914.¹⁴ Newburgh and his colleagues also presented convincing evidence to show the great improvement which occurs in diabetic patients after reduction of weight. Normal

glucose tolerance curves were obtained in nearly 75 per cent of 35 cases in which there was reduction to an ideal weight level. Improved tolerance was observed in half the remainder and in some cases with lesser amounts of weight loss. When the patients regained the original degree of overweight the impaired carbohydrate tolerance was invariably re-established. Therefore, simple weight reduction not only decreases the hyperglycemia and glycosuria of diabetes, but also in many cases actually converts the glucose tolerance to normal. Conversely, the clinical symptoms of diabetes mellitus are apt to recur when the excess weight is regained.

Since a normal carbohydrate tolerance can be achieved in many obese diabetic patients by weight reduction alone it is safe to forego insulin until it is certain that diet alone will not bring about aglycosuria.^{3c, 10, 11, 16, 17} Still, in actual practice diet treatment is frequently neglected and insulin prescribed instead. When obese patients are given insulin, without simultaneous insistence on dietary restriction, large doses (more than 100 units daily) of insulin may be required to correct even moderate hyperglycemia, although at least as good results can be obtained by diet alone. Moreover, patients are misled into the belief that insulin, not diet, is of primary importance to their welfare and, besides, they are subjected to a wasteful, unnecessary expense and the nuisance of frequent injections.

INDIVIDUAL THERAPY

The method generally employed in the treatment of obesity has been mainly pleading and exhortation mixed with threats of dire events. This approach meets with failure in a large percentage of cases. Recently, the appetite-depressant amphetamine drugs have come

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into vogue. Osserman and Dolger¹⁰ reported significant weight loss in 36 of 55 cases of obesity and diabetes treated with d-amphetamine sulfate, but one-third of these patients regained their original weight after the drug was discontinued. Our results with the anorexiogenic drugs have not been noteworthy.

It is fair to assume that attempts at weight reduction are unsuccessful in the average obese patient. Heretofore, in the Diabetes Clinic of Mount Sinai Hospital, our own results have been similarly unsuccessful. The patients, for the most part, were recalcitrant in following the recommended diets. Many of them remained obese for months and years, despite the persistent efforts of the attending physicians and dietitians.

GROUP THERAPY

One of us (J.I.G.) conceived the idea of group meetings with the sole purpose of re-emphasizing the importance of the diet in the treatment of diabetes. The role of diet in this disease had been stressed to these patients innumerable times and with those who comprised the initial group every other approach to dietary control had been exhausted. Essentially, it was an attempt to ascertain the effectiveness of group discussion in assisting these overweight diabetics, in whom all personal efforts had failed, to accept and adjust to the dietary restriction necessary to lose weight. Obviously, the prospects for attaining results in these particular patients were not bright. On our part, the effort to instill a better insight into the problems of overeating through a group approach was prompted solely by a desire to leave no stone unturned. The only requisite for membership in the group, other than the previous failure to lose weight, was mandatory weekly attendance.

RESULTS WITH GROUP THERAPY

Our first group was organized in September, 1949. Prior to the formation of these classes the patients had attended the diabetic clinic for periods ranging from one month to 15 years, with an average of 38.5 months. The Metropolitan Life Insurance Company "ideal weight" tables were utilized. At the onset a 1000 calorie diet was prescribed. Later the diet was curtailed to 900 calories. Successive groups were directed by each of the co-authors for periods of 12, 9 and 9 months respectively.

The duration of the weekly meeting is approximately one hour. Each session is introduced with a brief talk by the group leader on a subject such as the caloric

value of foods, the role of the emotions in obesity, or the adverse effects of obesity. The subject of the day stimulates the group discussion. A line graph of each patient's weekly weight is posted on a bulletin board, the ideal weight being clearly demarcated, so that each patient is well aware of his goal and the progress he or she is making in this direction. We consider it of importance that a patient who has failed to lose weight in the preceding week is requested to explain his failure to the others and required to bring in for review a detailed food diary which is read aloud and debated. When the group has finished its "cross-examination," excuses usually prove to be invalid.

To date 33 patients, predominantly female, have participated in the group program. At the onset they weighed from 9 to 157 pounds above their ideal weights. The average attendance in the clinic prior to joining the group was 2.6 years per patient (ranging from one month to 15 years). Few had shown any appreciable weight loss on the previously recommended weight reduction regimes. On our group program, 30 patients lost weight and 3 failed, which represents 90 per cent success. The weight lost during the period of treatment varied up to 50 pounds; the average weight loss was 14.2 pounds. It is noteworthy that, in the main, the patients maintained the weight loss successfully, after completing the group treatment. Some of the first group have now gone over 1½ years without regaining weight.

The most striking single result of the group therapy is the consistent weight loss obtained in a high percentage of cases previously thought hopeless because of failure to lose weight during the regular clinic visits with other methods of approach. The difficulties encountered in this group were enhanced by the fact that most of them were elderly, uncooperative, and of low intelligence; many had language handicaps and economic and sociologic problems which made it difficult for them to follow the dietary regime.

A purposeful attempt was made to create a spirit of camaraderie, an attitude of friendship whereby everyone becomes his "brother's keeper." Each group member develops an intense personal interest in the others, and listens to their problems. The successful participants explain to the class just how they had lost weight during the preceding week. The rise of a competitive spirit is inevitable, each member being anxious to match the results of the others. Frequently, a patient will absent himself from a meeting being embarrassed to face the others until he shows a weight loss. It is not uncommon, after a chiding by the others, to hear

this statement: "I'll show I can lose 3 pounds." Almost invariably such a patient will proceed to lose weight by the next visit and return to gloat over the individual who had goaded him. The medical group leader attempts to instill into the members a feeling of intimate, friendly interest in their problems. This serves to arouse a desire to please the leader so that the attitude of "I have to lose weight to please the doctor" pervades.

In every class there are at least one or two patients who immediately accept the prescribed diet and lose weight, so that even at the outset those who have difficulty can be shown rather than told how this can be accomplished. The patient with an obesity problem is especially skeptical of the doctor's advice regarding weight reduction. Frequently, we have encountered cases in which the advice of a neighbor, friend, druggist or radio announcer is preferred to that of the physician. With group therapy, this information can be introduced under the surveillance of the group leader who then directs it into the proper channels. Also, through group discussion, the usual false beliefs such as "obesity runs in my family, everything I eat turns to fat" and other ingrained untruths can be eradicated by demonstrating weight losses in some of the group members.

A factor in obtaining good results by this method is the value of constant repetition of every pertinent point during the class discussions. This was exemplified in the case of patients of low intelligence who had been obese for many years. Although it seemed that they did not comprehend the discussion, they nevertheless lost weight.

Another important consequence of this form of therapy is the gratification felt by the group leader. On observing the excellent results in dealing with those who had been so unsuccessful previously, an obvious feeling of enthusiasm arises which is contagious and transmitted to the entire group. All of this intensifies the efforts of both the patients and the group leader to secure even better results.

COMMENT

Group therapy has aroused much interest recently in psychiatric and general medical circles. Widespread use of this form of treatment came as a consequence of military necessity and a shortage of personnel in the treatment of neuropsychiatric conditions in the military services during World War II. Afterwards, it was applied extensively in civilian mental hospitals, Veterans' Administration hospitals, and, more recently, in psychi-

atric clinics and private practice. Alcoholics Anonymous also employ this technic and the effective use of group therapy with morphine addicts has been reported. Apparently medical group psychotherapy was originated in 1905 by Dr. Joseph H. Pratt and has been practiced since 1930 in the Boston Dispensary's "Thought Control Clinic" for psychoneurosis.

As emphasized by Bruch¹⁸ and well-known to most physicians, successful treatment of obesity depends on the cooperation of the patient. The patient who attends a clinic or sees his doctor regularly is more likely to adhere faithfully to a low calorie diet and obtain a satisfactory weight reduction. This opinion is supported by Hunter's¹⁹ figures which show that only 687 (27.5 per cent) of 2,447 obese patients attended the London Hospital Clinic long enough to be benefited. Of those in regular attendance 93 per cent lost weight. Other data appear to show that, whereas up to 50 per cent or more of obese persons may lose an appreciable amount of weight, less than 20 per cent successfully maintain their weight loss. The rigid discipline of the reduction diet creates a serious problem in self-indulgent patients who have overeaten all their lives.

Seeking effective methods of weight reduction, a pilot study was set up recently (1949) in Boston by the U. S. Public Health Service in cooperation with the Massachusetts Public Health Department.²¹ The New England Medical Center was chosen for this study because of its previous experience with group therapy. Twenty-six patients (nondiabetics) completed the course of treatment. At the beginning, they were from 4 per cent to 150 per cent overweight; the average number of pounds being 60. At the end of the treatment period the results varied from a gain of 2 pounds to a loss of 48 pounds. The average weight loss was 13.7 pounds; 19 of the 26 patients lost 10 or more pounds, an average loss of 15 pounds per patient.

Group therapy in dietary treatment has been reported rarely.²⁰ In a preliminary report of the present study the favorable results obtained in a predominantly older age group were presented.²²

Among our obese diabetic patients lack of appeal was the most common cause of breaking the reduction diet; the more normal the diet the better its psychologic effect. A positive approach is introduced by providing the patients with specific information concerning their diet. To the leader falls the task of discussing the problems related to overeating in an atmosphere conducive to a free and informal discussion. This should be done in a quiet room with the doors shut, free from such interruptions as the telephone. Ultimately, an atmos-

phere of friendly assistance is created for the patient.

In a therapeutic group such as ours, the novice soon gains the feeling of security through his acceptance by the physician in charge and the other members of the group. With a better understanding of his emotional problems through discussion, his fears associated with overeating are diminished. Assured of support through the sharing of common knowledge the patient learns to test reality situations and the fear of failure is thus lessened. Persons laden with guilt are no longer unique or isolated. Also, the group members are encouraged in their reduction efforts by the exchange of information pertaining to their mutual difficulties and by the accomplishments of the others. As the members become accustomed to each other, the leader deflects their dependence from him to the others. Because the members of the class are suffering from similar difficulties, competition and mutual support develop. Diabetic patients have an added incentive in that insulin injections can usually be avoided by weight reduction. Probably, their fear of the complications of this disease tend to produce better results than in the cases of obesity without diabetes.

At the outset, the majority of our patients believed they already possessed all the knowledge necessary for them to lose weight. Soon it became obvious that they required more assistance and knowledge. Participation in the group activities and discussions assisted their understanding and acceptance of the general physiologic and psychologic causes of overeating. Re-education and the assurance that it is possible to lose weight on a diet which is nutritionally adequate, without weakness or any other untoward symptoms, and with good prospects of avoiding insulin, are important factors. The patient's desire to lose weight, a clear understanding of the necessity for weight reduction and a thorough explanation of the principles of the diet all contribute to the success achieved.

Considering the poor results obtained with the individual approach, the effectiveness of group therapy in our previously recalcitrant diabetic patients is noteworthy. The results can be attributed to several factors: 1) competition within the group; 2) the knowledge that failure to lose weight cannot be glossed over lightly; 3) the intense education efforts of the medical group leader. As one patient stated: "I lost weight this time because I felt more than ever that the doctor and others are taking a close personal interest in me and I wanted to do it for him." Group therapy has the disadvantage of being applicable only to relatively few patients at one time. Still, the method yields results in

a large proportion of cases resistant to individual treatment. Our success with class discussion is attested to by weight losses, up to 50 pounds, in most of the 33 patients, the great majority of whom were considered recalcitrant beforehand. Some of them had been unsuccessful in attaining weight reduction by means of the usual forms of treatment over long periods of time, up to 15 years. Of 12 patients in our group who were taking insulin before joining the classes, 6 were able to reduce the dosage of insulin and 2 dropped it entirely, so that only 4 of the original 33 patients still required insulin. In Osseman and Dolger's series of 55 patients treated with the anorexigenic drugs, 84 per cent of the 31 patients taking insulin were able either to reduce the dosage or drop insulin entirely. The apparent contrast can readily be explained by the practice in our diabetic clinic, that is, to refrain from prescribing insulin except when there is ketosis, illness or other emergency, until it is clear that weight reduction will not correct the glycosuria. Consequently, based on the assumption that the diabetes would improve with weight reduction, most of our obese patients had not been taking insulin before.

SUMMARY

We believe our results can be attributed to the integration of practical dietetics and practical psychotherapy. The beneficial effects of class instruction illustrate how diabetic patients, by being brought together for free discussion, can solve a common problem without fear of derision. Competition creates a feeling of mutual understanding and confidence in the members of the group. In our opinion group therapy has opened a new avenue of approach to the successful treatment of diabetes mellitus.

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Treatment of Obesity as a Community Project

[The Louisville Nutrition Committee undertook a weight control project as a community service in the Fall of 1951. A half dozen agencies joined forces in a broad educational attack upon obesity. The following excerpts reveal some of their methods and results.]

Our logical and positive approach was by way of education, and a series of lectures and demonstrations was prepared for those interested in obesity and weight reduction. To stimulate interest through city-wide publicity, the local newspapers, the several radio stations, and the two television stations were most helpful in the successful launching of the program. Feature articles of interest in the daily papers, spot announcements regarding the weight reduction classes on the radio, and panel discussions and demonstrations on the television screen afforded considerable publicity.

In announcing the weight control classes to the public, notice was given to all that a physician's certificate was necessary for admission to any of these classes; such certification to indicate the need for weight reduction for reasons that would benefit the general health of the individual. This physician screening procedure aided in the detection of several cases not primarily due to overeating, insured optimal health in those participating in the program, and at the same time gained the approval and help of the medical profession generally.

Eighty-nine persons attended the first series of four classes extending over a period of three weeks. Seventy-seven or 86.1 per cent of these lost weight in significant amounts; two or 2.5 per cent maintained their initial weight, and one person gained weight. For this group the weight loss ranged between one-half and twelve and a quarter pounds for an average of five pounds per person during the first three weeks of the program. Follow-up studies were conducted at the end of 13 weeks with only 11 of the original 89 present. In this small group there was a 100 per cent individual weight loss, with the greatest loss amounting to 10 pounds and the smallest loss, one-half pound. At the end of 17 weeks 22 of the original 89 persons reported and 77.3 per cent had lost weight. One person had maintained weight and four had gained weight. The greatest loss was 22¼ pounds and the smallest loss, three pounds, giving an average of nine pounds loss per person. At the end of 26 weeks 19 of the original class were present; 79 per cent had lost, three persons had gained weight and one had made no change. The average weight loss was 11 pounds.

From A Weight Control Program at the Local Level, by John S. Llewellyn, M.D., Emily Bennett, Mary M. Hurley, M.P.H., and Mildred Neff, F.A.P.H.A., in the *American Journal of Public Health*, April 1953, page 433.

Clinical Usefulness of the Wilkerson-Heftmann Blood Sugar Test

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The need of a simple blood sugar test of practical clinical value has long been apparent. Since the number of diabetics in this country, recognized and unknown, approaches two million, it is evident that the great majority must of necessity receive their diagnostic and therapeutic services from general practitioners, often remote from laboratory facilities. The frequency of a high renal threshold for sugar among diabetics makes inadequate the sole use of urinary tests upon which many practitioners depend. On the other hand, a low threshold is not uncommon, among both diabetics or nondiabetics; patients with renal glycosuria are not infrequently being treated as diabetics for want of blood sugar determinations. The blood sugar tests in general use are technically complicated, time-consuming and too expensive for frequent use as a routine measure.

In 1948 Wilkerson and Heftmann¹ reported a capillary blood sugar test designed for screening purposes in diabetic surveys. This technic is extremely simple and rapid, requiring a minimum of equipment for its performance, and utilizing tablets both as reagents and for heating. This principle of the method consists in the reduction of ferricyanide, the unreduced portion of which oxidizes an iodide to form iodine, which in turn reacts with soluble starch to give a blue coloration to the solution. By incorporating a definite quantity of ferricyanide in the reagent tablet, the test indicates the glucose content of the blood as either above or below a specified level; a clear solution (showing complete reduction of the ferricyanide) indicates a glucose value above, and a blue solution (incomplete reduction of the ferricyanide) a value below, the predetermined level.

The protein in the blood solution, precipitated by other reagent tablets, is forced to the top of the test tube by the steam of the heating process, forming a cake which is easily scooped off. This eliminates a time-consuming filtration procedure. The test, moreover, shows *true glucose*, since all non-glucose reducing substances are eliminated in the process of protein precipitation. The equipment, together with a supply of tablets sufficient for 50 tests, is packed for convenient transport in a container the size of an ordinary cigar box. The test is rapid, requiring about five minutes for its performance, and so simple that a trained technician is not needed.

When the test became available for general use in 1949, provision was made for use of three blood sugar test levels: 180, 130, and 50 mg. per 100 cc. Each of these levels is of high clinical significance, namely, (1)—below 130 mg. per cent, the range of normal and hypoglycemic values, the latter supplemented by the 50 mg. per cent technic; (2)—between 130 and 180 mg. per cent, the range of satisfactory diabetic control; and (3)—above 180 mg. per cent, the range of unsatisfactory or poor diabetic control.

CLINICAL STUDY

With these facts in mind, the value of the Wilkerson-Heftmann test was explored under clinical conditions². Cases from the private practice of the senior author were first utilized, being selected only on the basis of the need of a blood sugar determination as an aid in clinical evaluation. Later a number of cases from the Outpatient Diabetic Clinic of the University of Nebraska, and fifteen juvenile diabetics in residence at the Springdale Camp were included. In the total study, more than 400 tests were made in caring for 110 ambulatory patients of all ages and with diabetes of

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all degrees of severity, and in twelve nondiabetic cases presenting diagnostic problems or used as normal controls.

Tests were made both for diagnostic and therapeutic purposes. In most cases arterial (capillary) blood was used; a number of venous blood specimens were also tested in special cases. A blue color was read as minus (below the designated level); a distinctly clear, colorless result was read as plus (above the level); and a light or indefinite blue coloration was read as plus-minus (assuming the blood sugar to be slightly above or slightly below the level).

DEPENDABILITY OF THE TEST

Wilkerson and Heftmann¹ admitted a possible error of 10 mg. per 100 cc. in their test. The result of fifty tests at the 180 level were obtained with determinations by a true glucose method (Somogyi-Nelson). There was perfect agreement in 46; in 21, in which the report was 170 or below, the color was blue; in 25 at 180 or above, the result was colorless; in four tests on the borderline (between 170 and 180) the result was either dark blue, light blue, or clear.

Haunz and Keranen³ found a "high degree of accuracy" in this test; they report only seven discrepancies among 200 capillary tests when comparisons were made with the determination of true glucose by using venous blood.

In sixteen cases we found complete agreement in all but four. In one case, where the Folin-Wu test was 107, the Wilkerson-Heftmann test indicated the blood sugar over 130 and under 180. In another case the blood sugar was 145 by the Folin-Wu test, and the Wilkerson-Heftmann test indicated plus-minus 130. A third case with the Folin-Wu blood sugar 195, the report by the Wilkerson-Heftmann method was over 130 and under 180. In a fourth case, in which Folin-Wu blood sugar was 114, the Wilkerson-Heftmann test indicated the blood sugar over 130 and under 180.

In interpretation of these results, one must keep in mind the fact that the Wilkerson-Heftmann test indicates true blood glucose value, whereas the Folin-Wu method includes nonglucose reducing substances, and thus the blood sugar report may be falsely high. Mosen-thal⁴ and Barry⁴ reported nonglucose reducing substances as high as 78; they found high and unpredictable variations. Haunz and Keranen³ in a study of 100 cases in which they compared the Folin-Wu and Somogyi-Nelson methods found non-sugar reducing substances ranging in amounts from 2 to 72 mg. per 100 cc. Both groups of authors found sugar reducing substances in excess of

30, in 38 per cent of their cases. It has been assumed that the non-sugar reducing substances could be arbitrarily taken to be 30, but the variations are now known to be much greater.

It can thus be seen that the lack of complete agreement of the Wilkerson-Heftmann and Folin-Wu tests does not necessarily indicate actual discrepancies in the last three cases cited above. In the first case, however, in which the value obtained by the Wilkerson-Heftmann method is greater than that obtained by the Folin-Wu method, this explanation cannot apply. The result may be considered an inaccuracy. Thus a single unexplained inaccuracy was found in a total of 32 tests by the Wilkerson-Heftmann method.

THE TEST AS AN AID IN DIAGNOSIS

There is general agreement that a fasting blood sugar in excess of 130 mg. per 100 cc. is presumptive evidence of diabetes. The converse is not necessarily true; a mild diabetic may have a normal fasting blood sugar. However, by checking the blood sugar two hours after an ample carbohydrate meal, the number of erroneous results can be minimized. At this time interval, a level below 130 is almost positive proof of the nonexistence of diabetes, whereas a reading above that level would at least place the diagnosis in a borderline status. Hence, if only a single blood sugar test is to be made, the best time is two hours after a meal. For more conclusive evidence, glucose tolerance curves may have to be employed. The Wilkerson-Heftmann test can be used for this purpose. Glycosuria with the blood sugar never above 130 must be renal glycosuria; elevation of the blood sugar over 180 persisting for two and three hours after taking glucose must indicate diabetes.

THE TEST AS AN AID IN THE TREATMENT OF DIABETES

Successful treatment of the diabetic patient depends upon clinical judgment supported by adequate laboratory aids. With ideal control, the patient should not only maintain weight and strength, but should also keep free from glycosuria and hyperglycemia. Tests of the urine may be sufficient guide in ordinary routine management with occasional blood sugar tests. However, when the renal threshold is abnormal, the routine use of blood sugar tests may become essential. In our Outpatient Clinic we regard a blood sugar of 150 by the Folin-Wu method as the ideal fasting level for patients requiring insulin. We believe that the blood sugar range of 130 to 180, two to three hours after meals, is additional evidence of satisfactory control. Blood sugar tests below

130 or above 180, in our opinion, required adjustments in diet or insulin or both. The Wilkerson-Heftmann test thus helps us to identify the desired range of blood sugar.

The past quarter century has witnessed a decided trend towards simplification in every phase of diabetic management, diet, insulin administration, and the tests for glycosuria and acetonuria. All of these simplified procedures have tended to permit a more normal life for the diabetic, and also the promotion of better control of the disorder.

A simple blood sugar test is in line with this trend and can fill an urgent need of many general practitioners and internists. Such a test, to have maximal value, should be technically uninvolved, requiring a minimum of equipment; it should not be time-consuming and so inexpensive that frequent use can be encouraged. The Wilkerson-Heftmann test meets all these criteria. The fact that it gives true glucose estimations enhances its value. The test set, including all necessary equipment and reagents, is sufficiently compact for easy transport and is thus made available for use in the home of the patient as well as in the physician's office. With this method either venous or capillary blood can be used in accordance with indications and needs. As shown by our study, it is useful both diagnostically and therapeutically in the management of diabetes.

That the test has its limitations is quite obvious. Of the fifteen children in the Springdale Camp during the 1951 season given tests several times throughout the day, only one showed sufficient stability of the blood sugar to permit evaluation. Such diabetics show fluctuation in the blood sugar to a notorious extent. This test does not indicate the full degree of fluctuation, since it merely indicates a level above 180.

The same situation may be found in diabetic emergencies. In diabetic coma, for instance, the test would have no value in guiding the therapy during the stages of highly elevated blood sugar although, as has been suggested by Haunz and Keranen³, it could be useful in differentiating between coma due to acidosis, hypoglycemic shock, or cerebrovascular disorders. Similarly, in febrile and post-surgical states, with fluctuations and unpredictability of the blood sugar, its usefulness would also be limited. Such eventualities, however, are mainly managed in hospitals where the laboratory facilities are likely to be available for more exact blood sugar tests. Exceptions may conceivably occur in thinly populated areas, with the patient too ill for transportation to a remote hospital, in which case the physician may be

forced to provide emergency treatment in the home.

The main limitation inherent in the test is the absence of blood sugar level definition within the areas of the blood sugar ranges. This does not necessarily constitute a serious impediment to its usefulness. In the normal and hypoglycemic range this limitation is not grave, although an additional level of 100, the upper limit of true glucose normals, might be desirable. Neither can there be serious objection to this lack of definition within the range of good diabetic control; we cannot concede important significance to the specification of particular levels between those of 130 and 180 mg. per cent. In the range above 180 mg. per cent, however, the deficiency may assume significant proportions, as indicated in the discussion of the management of diabetic emergencies. This defect can be corrected to a large extent by providing two higher levels, at about 250 mg. per cent and at 350 mg. per cent. Such can be accomplished either by developing additional reagent tablets or by a modification of the technic.

SUMMARY

The Wilkerson-Heftmann blood sugar test is rapid, simple, inexpensive and accurate. While it does not give the exact determination of the blood sugar it nevertheless enables one to know that it is in one of the four clinically significant blood sugar ranges—over 180; between 130 and 180; between 130 and 50; and under 50.

In 110 cases of diabetes and twelve cases of nondiabetic conditions or normal controls the test has been utilized to explore its value in clinical use. It can be concluded that the test is eminently useful in both diagnosis and guidance of therapy.

There are limitations inherent in the method, its chief deficiencies becoming obvious in the handling of diabetic emergencies. Two higher blood sugar testing levels are suggested to correct this fault.

In spite of its limitations, the test has been useful in a majority of diabetic problems and we do not hesitate to recommend it for general acceptance and wider use.

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Spontaneous Diabetes Mellitus in the Dog:

An Account of Eight Cases

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The literature on spontaneous diabetes in dogs is sparse and is confined almost exclusively to veterinary publications. As summarized recently by Schlotthauer and Millar¹, it contains reports of 42 cases including eight of their own. Clinical, chemical and pathologic data are sketchy. The frequency of the disease appears to be about one per thousand. It affects females predominantly and occurs from one year of age upward. All cases reported by Schlotthauer and Millar in which necropsy was performed showed either destruction of the pancreas, apparently by inflammatory processes, or, more commonly, extensive abnormalities of the islets of Langerhans. These consisted of diminution in number, hyalinization, fibrosis and, in one case, possibly hydropic degeneration. Those animals with the pancreas destroyed had fatty diarrhea and flatulence in addition to the usual thirst and polyuria. Renal lesions occurred frequently but are incompletely described.

CLINICAL FEATURES

The eight cases herein presented were pets referred by veterinarians. All but one Irish terrier and one chihuahua were mongrels. As indicated in Table 1, six were females. Only the chihuahua, aged 5½ years, was under 10 years of age. The estimated duration of diabetes to death or to date (June, 1953) varied from two weeks to fifty months. Five dogs were killed at the

request of the owners. One died of natural causes. Two, still living, have been under insulin treatment at home for forty-nine and eleven months, respectively.

The presenting symptoms in each case were the classical ones of diabetes—thirst, polyuria and loss of weight. Appetite was increased in some and diminished in others. Blindness had been noticed in more than half of the animals. (See Table I).

The outstanding feature of the physical examination was bilateral cataracts which were present at the first examination or developed later in all cases but one and may have been overlooked in this. The opacities were usually so marked as to prohibit visualization of the retina. Four dogs were still obviously obese despite a history of previous loss of weight. Three were in diabetic acidosis when first seen, one of them in frank coma, and all of these were treated successfully with insulin and intravenous infusions of 0.9 per cent sodium chloride solution and glucose. The amount of insulin given in the first 24 hours was from 20 to 40 units.

The dogs, when brought for examination, were placed in metabolism cages in the animal quarters of the hospital, where they remained for days or weeks. Some were returned at intervals for further study. They were fed once or twice daily either on the standard laboratory ration containing horse meat, bread, cod liver oil, brewer's yeast, alfalfa meal, bone meal, ascorbic acid and salt, or on commercial canned dog food. Six dogs were treated with protamine zinc insulin alone, one with protamine and regular insulin in separate injections, and one with NPH insulin. The insulin was administered after the morning feeding, the amount of food eaten, which was variable, being taken into account in arriving at the dose. The collection of urine specimens was often difficult during the first few days owing to the fact that the animals, being pets and therefore "house broken," would not void in the cage for periods up to 72 hours.

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TABLE 1. Spontaneous Canine Diabetes

Name	L,D	Sex	Age 1953 or at death (yrs.)	Weight (kg.)	Probable duration to exam. at U. of C. (months)	Total probable duration to date or death (months)
Wags	L	F	13	8.7	1	50
Corky	L	M	10	11.9	4	13
Mickey	D	M	11	7	0.5	0.5
Peggy	D	F	13	12.0	4	34
Penny	D	F	12	14.5	6	12
Teeny	D	F	5½	3.4	8	9
Tootsie	D	F	10	9.6	1	1
Blackie	D	F	12	±10.0	1	1

TABLE 2. Spontaneous Canine Diabetes

Name	Acidosis	Blood sugar mgm. %	Ser. cholest. mgm. %*	Urine Sugar (Qual. or %)		Adm. Urine Acetone	Final Insulin (u./day)	Duration of treatment to date or death (months)	Cataract
				Adm.	Rx				
Wags	+	363-178	226-576	+++++	+++++	—	20	49	+++++
Corky	0	288-106	235	+++++	0.9-5.6	+++++	20	11	+++++
Mickey	+	780-656	—	+++++	0	+++++	10	0.2	++
Peggy	+	372-170	462-641	+++++	0-++++	+++++	40	18	+++++
Penny	0	343-57	322-403	+++++	3.4-6.4	+++++	35	.4	++
Teeny	0	237-267	141	+++++	0.4-9.6	+++++	12	6-0.6**	07
Tootsie	0	398-257	—	+++++	1.7-7.3	+++++	26	0.5	+++++
Blackie	0	402-472	324	+++++	3.9-11.0	+++++	35	0.5	+++++

*Normal values for dogs average about 150 mgm. percent; range 120-200 mgm. percent.

**Treated 6 months with only 1-3 units insulin daily.

TABLE 3. Pathologic Findings in 6 Cases of Spontaneous Canine Diabetes

	Mickey ¹	Peggy ¹	Penny	Teeny ²	Tootsie	Blackie ³	No. abnormal
Scarce islets	0	+	0		+	0	2
Absent B cell granulation	?	?	+		+	+	37
Hydrop. degeneration	+?	?	0		+	+	37
Arteriosclerosis	+	+	+	+	0	+	5
Glomerular lesions	+	+	+	0	+	+	5
Tubular fat	+	+	+	+	+	+	6
Tubular glycogen	+	+	0	0	+	+	4
Liver fat	+	+	0	+	0	+	4
Liver glycogen	D ⁴	D	N ⁵	N	D	D	47

¹ Autopsy 12-20 hours after death.² Pancreas destroyed by abscess, <1 gm. remaining.³ No thyroid tissue found.⁴ D—deceased.⁵ N—normal.

The chemical data* are given in Table 2. Hyperglycemia was uniformly present, being most marked (blood sugar 780 mg. per cent) in the dog Mickey with both diabetic acidosis and cirrhosis of the liver. The urine was strongly positive for sugar and acetone in all except one case in which the latter was not determined. Values for serum cholesterol were elevated in all cases in which such analyses were made, with the exception of the dog Teeny whose pancreas had been destroyed with resulting steatorrhea.

As illustrated in Table 2, the treatment of these ani-

*Blood glucose was determined by the method of Nelson², quantitative urine glucose by the method of Brodersen and Ricketts³, and serum cholesterol by the method of Sperry and Brand⁴.

mals in the laboratory, the unpredictable relationship of insulin dosage to blood sugar response, due in part to irregularities in eating, and the brief time allowed by the owners for stabilization, made it impractical and undesirable to strive for strict control of glycosuria. In treatment at home, the owners were taught to test the urine, which they collected by whatever means they could devise, and insulin dosage was regulated accordingly, but because of the danger of hypoglycemia from variable activity, no attempt was made to keep the urine sugar free. It is evident, therefore, that the maintenance doses of insulin, which ranged from 10 to 40 units daily for different animals, fell short of the amounts that would be required for good control.

Of the five dogs killed at the request of their owners,

four were dispatched with nembutal given intravenously and one with "gas" at the hands of a veterinarian. The dog dying of natural causes was found to have a massive infarction of the left cerebral hemisphere. Necropsy was performed in all six cases, in four immediately after death and in two, unavoidably, from twelve to twenty hours afterward.

PATHOLOGY

The principal pathologic findings are summarized in Table 3.

The *pancreas* was grossly normal in all cases except that of Teeny, in which the organ had been almost totally obliterated by an abscess, less than one gm. of recognizable pancreatic tissue remaining. Microscopically, one case showed fibrosis, hemorrhage and fat necrosis. The islands of Langerhans were scarce in two cases (Peggy and Tootsie). In two cases (Peggy and Mickey) post mortem autolysis obscured the finer details, but in the remaining three with the pancreas grossly intact, beta cell granulation was virtually absent*. Two cases, each with diabetes of only one month's duration, presented classical hydropic degeneration of the islets and of the duct epithelium (Figure 1).

A third case, with symptoms of only two weeks duration, showed similar alterations, but the acinar cells also were filled with vacuoles, a fact which, together with the presence of hepatic cirrhosis and the long interval after death at which necropsy was performed, makes evaluation of the islet lesions difficult. It is believed, nevertheless, that they represent genuine hydropic degeneration. After these changes had been observed in tissues fixed with Bouin's solution, sections from the original blocks were washed in water, brought up through the alcohols and stained for glycogen. In two of the three cases the results were negative but the third showed considerable deposition of glycogen in the islets. Thus, of the five dogs with the pancreas present, four definitely and one probably showed extensive and severe abnormalities of the islands of Langerhans.

Arteriosclerosis was present in five of the six dogs. It was demonstrable grossly in four of the five aortas, chiefly although not exclusively in the abdominal portion, but was nowhere striking in degree. Microscopically, these lesions consisted of either nodular or plaque-like fibrous thickening of the intima without calcium or lipid infiltration or rupture of the internal elastic

*Tissue stains on which these observations are based were made with chromium-hematoxylin and phloxin according to the method of Gomori⁵.

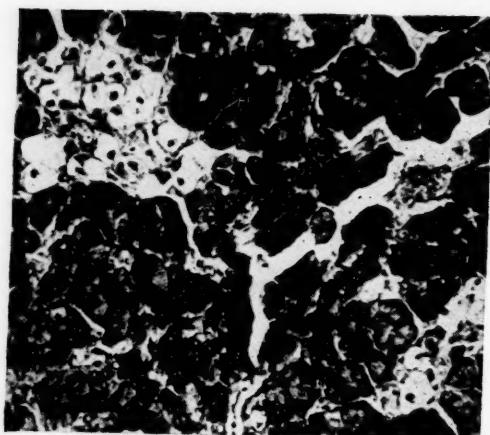


FIGURE 1 Dog Blackie. Hydropic degeneration (large clear cells) of islands of Langerhans and small bile ducts. In specially stained sections these cells were found to contain glycogen. Gomori's chromium-hematoxylin and phloxin. (X 225).



FIGURE 3 Dog Penny. Carotid artery at junction with aorta. H & E (X 41).



FIGURE 5 Dog Penny. Glomerular lesions. Spheroid bodies containing fine lipid droplets and hyaline are well shown. See text. Mallory's azan. (X 120).

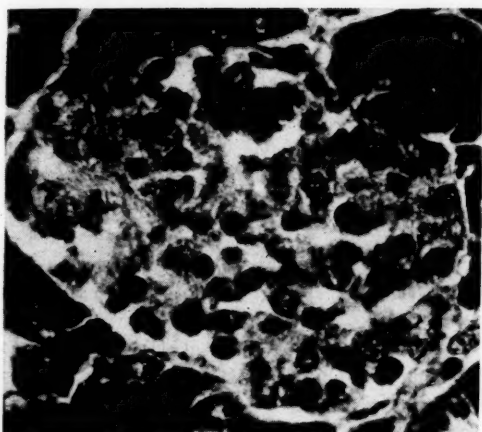


FIGURE 2 Normal dog's islet of Langerhans. The numerous beta cells are filled with fine granules which appear gray in the photograph. Gomori's chromium-hematoxylin and phloxin. (X 700).

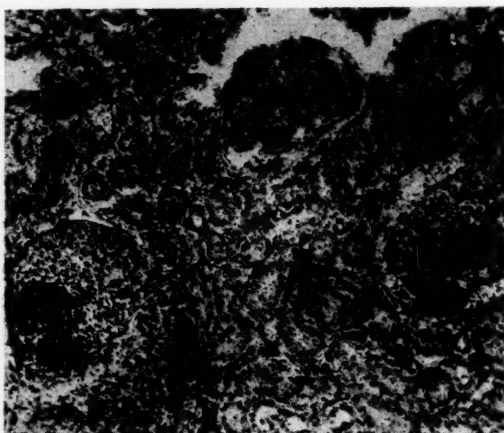


FIGURE 4 Dog Penny. Fat (dark areas) in glomeruli. Sudan III. (X 100).



FIGURE 6 Glomerular lesions in human case of intercapillary glomerulosclerosis. Lesions are more advanced than those in Figure 5 but are qualitatively similar. Mallory's azan. (Approx. X 150).

lamella. In several cases the larger branches of the aorta were similarly involved (Figure 3) and in these situations lipid material, while sometimes present in the media, was encountered only once in the intima. In only one dog, which was athyreotic, were the coronary arteries definitely involved, and here again there was nothing to suggest true atheroma. For the most part the vascular lesions could not be distinguished from those occurring in nondiabetic old dogs. The medium sized and small arteries of the brain, thyroid, pancreas, spleen, kidney and adrenal showed no abnormalities.

A word of caution is indicated about the interpretation of sections made through the aortic ring. In the normal dog, a rim of calcareous tissue runs around the ring just inferior to the attachment of the valve cusps. This has a roughly triangular shape in cross section and stains purple with hematoxylin and eosin. It should not be mistaken for a degenerative lesion.

Kidneys. In only one case was there encountered the extensive interstitial nephritis to which dogs are often subject. This animal, as might be expected, and four of the remaining five, showed various forms of glomerular lesions. For the most part, these consisted of thickening of Bowman's capsule, often eccentric, and atrophy of the capillary tuft in from ten to thirty per cent of the glomeruli. Fibrosis or hyalinization of the tuft was present in several cases but not extensive, and was not dissimilar to the changes found in nondiabetic old dogs. In two cases, the glomeruli contained accumulations of fat (Figure 4). In one of these (Figure 5) the lesions were striking and widespread and, except for the absence of typical hyaline bodies, resembled those described by Kimmelstiel and Wilson in diabetic patients (Figure 6). The azan section of this kidney may be described as follows: "Some glomeruli show atrophy and fibrosis. In many of these the parietal layer of Bowman's capsule is tremendously thickened, often eccentrically, in laminae. Many tufts show one or more capillary loops forming lobular masses, sometimes involving the entire tuft, swollen by large pale cells, presumably endothelial cells. These are laden with lipid and apparently occlude the lumen of the capillary. Surrounding these cells or groups of cells are layers of connective tissue which is sometimes hyalinized. Parts, or entire tufts, are thus converted into fibrotic multiloculated spaces containing cells. These lesions vary in fibrous content from slight to very great. The latter type form fibrosed glomeruli which are similar to the usual fibrosed glomeruli. There is no change in blood vessels except that the glomerular lesions appear almost or completely avascular."

Fatty infiltration of the renal tubules was present in all six cases. In four, including two in which necropsy was performed from twelve to twenty hours after death, the tubules contained considerable glycogen.

The liver was very cirrhotic in one dog, and in this case and three others contained large to moderate amounts of fat. Glycogen was normally abundant in two cases and diminished in four, including the two in which necropsy had been delayed.

Endocrine system. By the greatest misfortune all the pituitary glands were lost during tissue preparation. They uniformly appeared normal at necropsy. The adrenals in each case showed greater or less degrees of nodular hyperplasia, a normal finding in the old dog with, in some cases, a decrease in lipid. The thyroid was normal except in the one case in which it was absent. In this case the body fat was very pale and edematous and the fibers of the myocardium were rather widely separated by clear spaces. The possibility that the latter might be artifact cannot be excluded although sections of other hearts similarly treated did not show it. The ovaries and testes, when present, showed nothing relevant to the present subject.

The retinæ were dissected from the globes of the eyes in all but one case, mounted flat on slides after the method of Friedenwald⁶ and stained with the periodic acid Schiff reagent. Careful search revealed no abnormalities of the vessels or the retina proper.

INSULIN CONTENT OF PANCREAS

In four cases the pancreas removed at necropsy was frozen in carbon dioxide snow or minced into acid alcohol and sent to Dr. G. A. Wrenshall at the University of Toronto for the measurement of extractable insulin. These analyses (Table 4), in agreement with others made by Doctor Wrenshall⁷, show a marked diminution of extractable insulin in the diabetic as compared with the nondiabetic dog's pancreas.

DISCUSSION

In dogs, spontaneous diabetes differs in no important respect from permanent experimental diabetes produced by alloxan, pituitary extracts or subtotal pancreatectomy. Perhaps it is too much to say that it does not differ materially from human diabetes, but the resemblance, with the possible exception of the vascular complications, is close, even in its predilection for middle aged or elderly females.

Common to all forms are the chemical disturbances of hyperglycemia, glycosuria, hypercholesteremia and,

in severe cases, ketoacidosis. The high incidence of cataract in the present series is duplicated in dogs with poorly controlled experimental diabetes regardless of age and is paralleled in young patients in whom the disease has been neglected. In all of these situations opacities of the lens have been observed to develop in a matter of weeks. The presence of glycogen and fat in the renal tubules, and the infiltration of fat and the depletion of glycogen in the liver, are seen in both human and canine diabetes, whatever the pathogenesis, following periods of uncontrolled glycosuria.

Concerning arteriosclerosis, it is hard to make comparisons for the reason that the lesions here described were found in old dogs, and such animals, even without diabetes, are known to be similarly affected. Indeed, true atherosclerosis, which was not observed in the present cases, has been described in presumably nondiabetic dogs of advanced age⁸. In view of the fact that it takes diabetic patients from ten to twenty years to develop atherosclerosis, such lesions could scarcely have been attributed to diabetes, even if they had been found, in these animals with glycosuria of only a few months' duration. Perhaps similar reasons account for the complete absence of retinopathy, although it must be admitted that this may be only a matter of species difference. Retinopathy hasn't occurred in dogs with uncontrolled experimental diabetes of more than three years⁹.

In all reported cases of spontaneous canine diabetes which have been adequately studied there has been unmistakable histologic evidence of failure of the insulogenic apparatus. When the pancreas has been extracted for insulin, minimal amounts have been found. These observations are consistent with the fact that permanent diabetes has never been produced in animals except by damaging the beta cells. It is of interest that in the present cases (illustrated in Table 4) hydropic degeneration of the islets, generally recognized as an early

TABLE 4. Correlation of Extractable Insulin with Histology of Pancreas

Diabetics	Scarce Islets	B cell granulation absent	Hydr. Degen.	Extractable Insulin*		
				u/Gm.P	u/Kg.	% of Control
Peggy	+	?	?	.104	.20	1.8
Penny	0	+	0	<.04	<.05	< 0.9
Tootsie	+	+	+	>.45	>2.07	>19.0
Blackie	0	+	+	>.097	>.29	> 2.8
Controls						
Phem.	0	0	0	2.89	8.15	100
D-190**	?	?	?	12.3	13.3	

*Dr. G. A. Wrenshall

**No histology available

specific lesion of diabetes, was present in the three dogs with symptoms of less than one month's duration. The advanced age of the dogs showing this lesion is at variance with experience in diabetic patients, in whom hydropic degeneration and a very low concentration of pancreatic insulin are found much more commonly in young than in elderly individuals. The appearance of the islets, however, and the presence of glycogen therein, strongly suggest a pathogenetic process which is common to both species.

The cause of beta cell failure in dogs is no more apparent than in man. The pituitary bodies, while not available for microscopic examination, were grossly normal when removed. It will be recalled that this organ shows no consistent change in human diabetes. The adrenal glands, although exhibiting nodular hyperplasia, were not significantly different from those of nondiabetic old dogs. Nothing is known about the genetic aspects of diabetes in this species.

Of particular interest are the glomerular lesions in the case of Penny. This pedigreed Irish terrier, aged 12 years, had had symptoms of diabetes for six months before treatment was begun and had been incompletely treated for another six months with from 15 to 35 units of insulin daily. Proteinuria, which had been absent on several previous occasions, appeared in large amounts (4+) shortly before the dog was killed. Blood pressure was normal. While it cannot be stated categorically that the lesions are identical with those of intercapillary glomerulosclerosis in man, they are certainly similar, and indeed more so than any glomerular changes reported in experimental canine diabetes^{9,10}. To the best of our knowledge, they have not been described in nondiabetic dogs. If they be considered as the counterpart of the human lesions, then certain questions arise: (1) Are twelve months of poorly controlled diabetes enough to have produced such changes? (2) If so, why have they not been found to this degree in dogs with uncontrolled experimental diabetes of more than three years' duration? (3) Is it possible, as has been hypothesized for man, that spontaneous diabetes carries with it the tendency toward vascular disease and that hyperglycemia and its concomitants alone, although perhaps augmenting it, do not actually cause it? (4) If this is true, why did true atherosclerosis, as distinct from fibrous arteriosclerosis, not appear in the present case? (5) Since the Kimmelstiel-Wilson syndrome in patients rarely occurs without retinopathy, why was the retina spared in this dog? Obviously, further studies are needed to get these answers.

SUMMARY

Spontaneous diabetes in dogs closely resembles clinically, chemically and pathologically the experimental form of the disease and in many respects is similar to diabetes in man. It is apparently associated in all cases with extensive histologic abnormalities of the islands of Langerhans or of the pancreas as a whole, and with a marked depletion of extractable pancreatic insulin. Fibrous arteriosclerosis, not atherosclerosis, is the rule and is doubtless related more to the age of the animals than to the influence of diabetes. In one case glomerular lesions scarcely distinguishable from those of intercapillary glomerulosclerosis in man have been found and described.

It is a pleasure to acknowledge the assistance of Nathan R. Brewer, D.V.M., in procuring diabetic dogs.

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DISCUSSION

CHARLES H. BEST, M.D. (Toronto): There is a fascination about the study of spontaneous diabetes in animals, which is not associated with that produced in the same species by pancreatectomy, alloxan, somatotropin or other hormones. This special interest lies in the fact that some new mechanism or association of causative factors might be revealed which would throw new light on the spontaneous diabetes of man. The mere fact that the diabetes of man and animal can be accurately labelled with the same term—spontaneous—implies a similarity in etiology which, of course, has as yet no established basis whatever.

I had the pleasure of hearing a part of the findings

of Doctor Rickett's group when he presented them at a special meeting of The Toronto Diabetes Association last January. Dr. Ricketts and Dr. Gerald Wrenshall, of our department, have kept in close touch with each other. Doctor Wrenshall has studied four cases of spontaneous diabetes in dogs and may well wish to amplify my remarks. What we are all most anxious to find is the primary etiological lesion or a reversible lesion in the human diabetic. The careful study of the spontaneous diabetes of dogs is one very useful avenue to follow. Doctor Wrenshall is quite rightly anxious to locate and study a form of diabetes in animals which duplicates the human picture of maturity onset diabetes in which the pancreas retains nearly half its normal insulin content. It is, of course, possible that compensating processes, perhaps hormonal in nature, frequently arrest the destruction of insulin-producing tissue at a certain stage in the human subject and that does not happen in the dog. The primary etiological process might, however, have been the same in the two species.

I can think of plenty of further studies which vigorous and well trained young men could conduct. As you all know, a beginning has been made in the detection of the pre-diabetic state in humans. A comprehensive study of this vital matter has not yet been reported. What combination of procedures in a partially depancreatized dog would detect the fact that half his pancreas was missing? How much pancreas must be removed before our most searching combination of tests reveals the irreversible lesion? As Dr. Lukens has observed, some dogs may develop frank diabetes after removal of half their pancreas. This is not usual in my limited experience and Doctor Wrenshall, who has recently taken a "statistical" look at the data collected by Dr. Frederick M. Allen, may wish to comment. Further work of this type in dogs, using all our present aids, might well help to determine the most productive test procedure for the detection of the prediabetic state in human subjects. When these procedures have been established they might also be applied on a large scale in many laboratories with the objective of detecting an earlier phase of the condition which may lead to spontaneous diabetes in dogs. Thus Dr. Ricketts and his colleagues and Doctor Wrenshall might augment their, shall I say, veterinary or clinical practices and might have opportunities to study this phenomenon of spontaneous diabetes at an even more interesting phase.

G. A. WRENSHALL, M.D. (*Toronto, Canada*): It has been interesting to hear further of Doctor Ricketts' work and Doctor Best's comments. I have little to add,

except to say that we have now been able to study the insulin content of the pancreas in seventeen cases of growth onset diabetes. In sixteen of these subjects, there was not more than a trace of insulin. The seventeenth was very interesting; the subject had severe cysteinosis.

In cases of maturity onset diabetes, the insulin content of the pancreas may average 50 per cent normal, but this represents a wide spectrum of values all the way from traces up to above normal in several cases. I do not think that cases of maturity onset diabetes are a homogeneous group but apparently growth onset diabetes shows a characteristic response.

ELLIOTT P. JOSLIN, M.D., (*Boston, Mass.*): I should like to ask about clinical data for these dogs. How many of them were fat before they developed their diabetes? I should like to know about their heredity. What a marvelous opportunity to see whether it is transmitted from one generation to another. How many of them have grandchildren puppies? I think there is a splendid opportunity to study the effect of diet, and to watch how those who were treated most carefully compared with those who were left alone.

HOWARD F. ROOT, M.D., (*Boston, Mass.*): Can Dr. Wrenshall say if there have been any cases in the group with onset of diabetes in the growth period in which there has been early in the course of the diabetes any considerable amount of insulin in the pancreas?

G. A. WRENSHALL, (*Toronto, Canada*): There seems to be no difference between cases of early diabetes just detected and the cases treated for a long time with insulin. Apparently, the diabetes results from insulin-lack even in the early detected cases.

QUESTIONER: Was any attempt made to breed these diabetic dogs?

HENRY T. RICKETTS, M.D., (*Chicago*): I have been asked how many dogs were fat. There were four only which were obese at the time we saw them, or which had been obese according to the owners' statement in the past; not as one might expect to find. Some, however, were still quite fat when we found them, despite the statement they had lost weight.

Concerning heredity, these dogs were for the most part mongrels, and we have no information on their background. As to the question of breeding them, which ties in with Dr. Joslin's question, it was not practical. The owners insisted that the animals be disposed of. They did not want them around the house themselves, nor did they want us to keep them and "experiment" on them. So that we were able to secure the autopsy only by promising to dispose of the animal.

Factors affecting The Islets of Langerhans

R. E. Haist, M.D., TORONTO

Diabetes results from the fact that not enough insulin is available to tissues. This may be caused by an *absolute deficit* in insulin secretion, as when the islets are destroyed or the pancreas removed, or it may result from a greatly *increased requirement* for insulin such as might occur in the first phase of the administration of diabetogenic pituitary extracts. It is conceivable, too, that under some circumstances insulin might be inactivated before reaching the tissues, or that the utilization of insulin by the tissues might be interfered with in some way. Whatever the underlying factor or factors may be, if insulin injections alleviate the condition then we are forced to the conclusion that a *relative* deficiency of insulin must be the direct cause of the changes characteristic of the disease. If this is so, then it is of some interest to learn as much as possible about the insulin-secreting structures, the islets of Langerhans; and it is of some importance to discover how their activity is regulated; how this function may be stimulated or depressed; or by what means their cells may be damaged and destroyed. The means by which the islet cells may be destroyed comes more properly under the heading of experimental diabetes, so the discussion here will be confined largely to a consideration of the regulation of the activity and the growth of islet cells. This regulation becomes especially significant when we appreciate that much islet tissue is still present in many adult diabetics.¹

The islets constitute about 1 per cent of the weight of the pancreas, and while we ordinarily think of them as fixed structures, they do actually exhibit a remarkable lability associated with the need for insulin. It should be pointed out that growth of the islets is one evidence of islet stimulation. As a rule, those factors causing islet growth are factors which would appear to cause secre-

tion also. In young, growing animals, certain factors stimulate the islets to grow and secrete. In the sensitive adult dog, the same factors also stimulate growth, and secretion, but the stimulation may be excessive in relation to the growth, and the islets degenerate and the animal becomes diabetic. While stimulation of the islets is necessary for normal activity and growth, it must always be borne in mind that excessive stimulation may lead to exhaustion of the islet cells, degeneration of those cells and diabetes. Thus, stimulation of the islets under one set of circumstances leads to an increase in islet mass and an increased potentiality for insulin secretion, whereas under another set of circumstances strong stimulation of the islets may lead to their exhaustion and degeneration. The point to be made at this time is that growth of the islets is one evidence of islet stimulation.

FACTORS INFLUENCING GROWTH

Many factors influence islet activity and growth, but for the most part these can be grouped as dietary and hormonal factors. Among the dietary factors the first one of importance is caloric intake.² If the intake of a balanced diet is so reduced that the individual fails to gain weight and the body weight remains constant, then the islets also fail to grow. If to the basal diet, equicaloric supplements of carbohydrate, protein or fat are added, then the animals receiving the carbohydrate or protein supplements show a significant increase in islet tissue, whereas the animals with the fat supplement do not.³ Both carbohydrate and protein stimulate islet growth,⁴ whereas fat does not. Similar conclusions concerning the effect of diet on islet activity have been derived from experiments concerning the insulin content of the pancreas and other studies.^{5,6} The conclusion from the diet work is that in order to have normal activity and growth of islets there must be a sufficiency of calories and a sufficiency of carbohydrate or protein (from which carbohydrate may be formed). If the caloric intake is

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reduced, or the carbohydrate intake is reduced, then islet activity and growth are depressed, whereas increasing the carbohydrate intake stimulates islet activity and growth. Excessive stimulation of the islets can be prevented by the reduction of caloric intake or restriction of carbohydrate supply.

Other evidence for a stimulating effect of carbohydrate is the finding that the continuous intravenous infusion of glucose occasions a greater than normal growth of the islets.^{7,8} This enhancement of islet growth is obtained despite the fact that, after six to 24 hours, the blood sugar level may be back within the normal range. While there is good evidence that an elevation in blood sugar level may stimulate the secretion of insulin, a marked elevation of blood sugar level does not seem to be the only stimulating factor. In these infusion experiments, the stimulation seems to be related to the total amount of carbohydrate administered in a given period rather than to any large change in blood sugar level.

HORMONAL FACTORS

The hormonal factors influencing the islets are numerous. Insulin, the hormone produced by the islets, when given in large amounts depresses the growth of the islets and the production of insulin by their cells.⁹ Indeed, experimentally, this depression of islet activity may under certain circumstances be great enough to produce a temporary diabetic state.

One endocrine gland whose functions seem in many, though not all, respects to be antagonistic to that of the *endocrine pancreas* is the anterior pituitary gland. When certain of its products are present in excess, more insulin is required or diabetic effects are observed. In sensitive adult dogs or in partially depancreatized animals of several species, including the rat, certain anterior pituitary extracts are diabetogenic.^{10,12} The diabetogenic effects can be prevented by giving insulin.^{13,14} In the intact rat the extracts do not produce diabetes, presumably because the islets themselves can sufficiently increase their insulin supply. The islet tissue in the rat is increased by daily injections of crude saline extracts of the anterior pituitary gland.^{15,16} Even in dogs in which these extracts are diabetogenic, signs of new formation of islet, acinar and duct cells are evident.¹⁷ The increase in islet tissue in the rat, and signs of mitotic activity in the islets in the dog, have been taken as evidence of a pancreatropic effect. While it is true that pituitary extracts stimulate the islets, removal of the pituitary does not lead to atrophy of the islets.¹⁸ Hence, a true tropic effect on the islets has not been established.

However, the removal of the pituitary gland does prevent the islets from growing, but it also prevents the body as a whole from growing.

The crude pituitary extracts used to stimulate the islets contain a great variety of factors. The anterior pituitary gland influences the adrenals, thyroid and gonads through tropic principles, as well as peripheral tissues in general through the growth hormone. Figure 1 shows the effects of some highly purified pituitary principles on islet weights, and compares these with the effect of a crude saline extract of the anterior pituitary

ISLET WT. PER CENT CONTROL

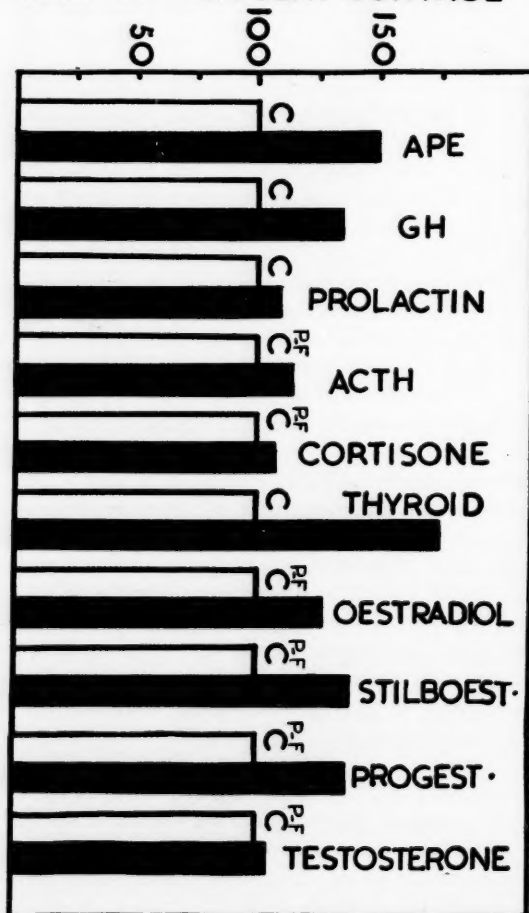


FIGURE 1 The effects of some pituitary, adrenal, thyroid and gonadal substances on islet weights in intact rats.

Key: APE = anterior pituitary extract, GH = growth hormone preparations, ACTH = corticotropin. Stilboest. = diethyl stilboestrol, Progest. = progesterone. Islet weights in control animals are represented as 100.

gland.^{16, 19, 20} Where the pituitary tropic principles were not tried, the effects of certain hormones of their target organs have been tested. Thus thyrotropin was not tried, but the effect of the administration of desiccated thyroid gland was investigated.²¹ Gonadotropins were not tested but the effects of certain sex hormones were studied²².

To permit comparisons, the islet weights in the control animals for each experiment are shown as 100 in each instance and the test values scaled accordingly. Crude anterior pituitary extract (APE), growth hormone preparations, thyroid, estradiol benzoate, diethylstilboestrol and progesterone all caused significant increases in islet tissue. Corticotropin (ACTH) did too, but although the increase was significant it cannot be considered extensive.* The effects of prolactin, cortisone and testosterone were not significant in the intact animals.

To see if these effects were mediated through the pituitary gland, the pituitary was removed and certain of the materials were tested again.

All the substances shown in Figure 2 were effective in causing significant increases in islet tissue in hypophysectomized rats. Some of these caused the body weight in the hypophysectomized animals to increase; some of them had little effect on body weight; some caused the body weight to fall.

*The effect is greater if given by continuous intravenous infusion.

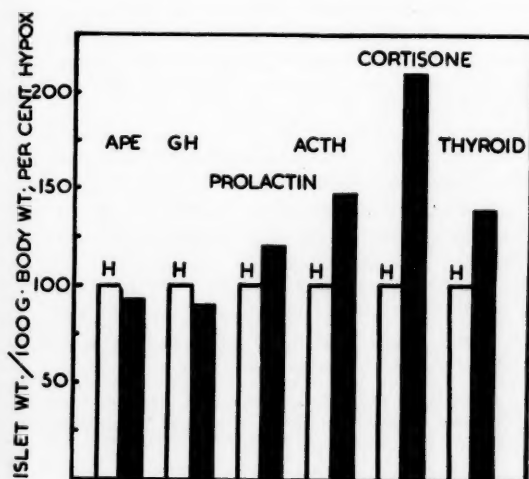


FIGURE 2 The effects of some pituitary, adrenal and thyroid substances on islet weights in hypophysectomized rats.

Key: Hypox. = hypophysectomized, APE = anterior pituitary extract, GH = growth hormone, ACTH = corticotropin. Islet weights in control animals are represented as 100.

When the islet weight is expressed in relation to the body weight (Figure 3) then we see that in comparison with the influence on the body as a whole, cortisone, corticotropin and thyroid administration have very profound effects on the islets. Of all the stimulating factors, thyroid seems to be particularly interesting and to have a good effect in intact and hypophysectomized rats,—an effect not related to a change in body weight.

The pituitary is not essential for the maintenance of the endocrine pancreas, for considerable periods of time at least, but the pituitary is necessary for the growth of the islets. It is also necessary for growth of the animal as a whole. Islet growth may be related to the growth of the animal as a whole and to the effect this has on insulin requirements, rather than to any specific effect of the pituitary apart from this. Other things which prevent body growth, such as the restriction of caloric intake, also prevent islet growth. However, with some materials islet growth is out of proportion to body growth and it may be that islet growth and body growth are quite independent. The information presented in this paper is summarized in Table 1.

SUMMARY

The fact that several different substances seem capable of stimulating islet growth makes one feel that their effects are probably brought about through some final

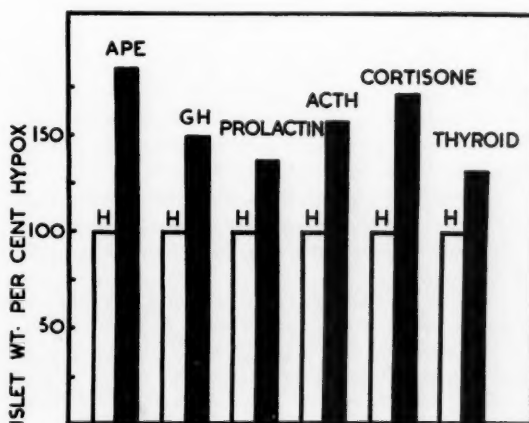


FIGURE 3 The effects of some pituitary, adrenal and thyroid substances on the islet weights per 100 g. body weight in hypophysectomized rats.

Key: Hypox. = hypophysectomized rats, APE = anterior pituitary extract, GH = growth hormone, ACTH = corticotropin.

TABLE 1 Factors Reducing Islet Activity and in Young Rats Depressing Islet Growth

1. Restriction of caloric intake. Restriction of carbohydrate intake.
 2. Administration of large amounts of insulin.
 3. Removal of the pituitary gland.
- Factors Stimulating Islet Activity and in Young Rats Increasing Islet Growth

	Condition of Animal	
	Intact	Pituitary Removed
1. High carbohydrate intake.		
2. Continuous injection of glucose.		
3. Injections of anterior pituitary extract:	+	+
4. Injections of growth hormone preparations:		
5. Injections of corticotropin (ACTH)	+	+
6. Injections of cortisone:	Not sig.	+
7. Thyroid administration:	+	+
8. Estradiol benzoate:	+	Not done
9. Diethyl stilboestrol:	+	Not done
11. Testosterone:	+	Not done
10. Progesterone:	Not sig.	Not done

common path. It seems altogether likely, from other work, that the materials which stimulate the growth of the islets do so because they increase the need for endogenous insulin, though the manner in which this requirement is transmitted to the pancreas is not known.

In conclusion, it should be pointed out again that excessive stimulation of the islets under some conditions can lead to degeneration and finally to disappearance of the insulin-secreting cells. It should also be emphasized that those factors reducing islet activity can prevent this excessive stimulation and protect the islets.

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A New Technic for the Detection of Hidden Diabetes

Induction of Hyperglycemia by Feeding Glucose after Dietary Preparation

Hugo T. Engelhardt, M.D., James A. Greene, M.D., V. C. Baird, M.D. HOUSTON, TEXAS

The recent mass surveys of the population for diabetes mellitus have caused widespread interest. In many instances the surveys have been conducted by examination of the urine for glycosuria. In others the preliminary screening survey has been based upon the presence of glycosuria, followed by blood sugar estimation one to 1½ hours postprandial without previous dietary preparation. As an example, Blotner¹ studied the results of the urine examination of 69,088 men examined for military service, finding two per cent exhibiting glycosuria. In glucose tolerance tests on 479 selectees without previous dietary preparation, he found diabetic tolerance curves in 251 cases or 52 per cent of those tested. Of the 1,383 with glycosuria, 340 or 24.1 per cent knew they had diabetes or glycosuria previously. Fitcher and Sauve² attempted to detect diabetes by giving 75 grams of glucose to ambulatory patients and looking for glycosuria. None of these patients, however, were given previous dietary preparation for the test.

It is generally accepted that the presence of glycosuria alone does not warrant diagnosis of diabetes mellitus. On the other hand, persons with diabetes do not necessarily show glycosuria. That an individual with mild diabetes mellitus may be overlooked in a preliminary screening by testing the urine, is therefore, a good possibility. It was for this reason that

employees of a large industrial concern who had previously had from two to twelve periodic physical and laboratory surveys by the staff of the medical division of the company were studied for the presence of diabetes mellitus.

SCREENING METHOD

Tests were made on 500 employees with an average age of 39.8 years. Each subject was given a diet of 2550 calories, containing 300 gm. of carbohydrates, 90 gm. protein, and 110 fat, for a minimum of three days. On the morning of the test the subject ate the breakfast of the diet which contained 118 gm. of potential glucose. He then ingested 50 gm. of glucose in solution. He presented himself at the laboratory one hour later. Venous blood was taken for sugar estimation by the Folin-Wu technic; a specimen of urine was collected and examined for glucose.

All individuals showing a screening blood sugar of 150 mgm. per 100 cc. or higher were subjected to a three-hour glucose tolerance test (1.75 gm. of glucose per kgm. of body weight, given in one dose). Prior to the glucose tolerance test, the subjects were instructed to follow the same diet as that prior to the screening test.

RESULTS

In the screening test, 62 individuals or 12.4 per cent exhibited glycosuria from a very slight trace to

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3 plus. Of these, forty or 8 per cent had a low renal threshold. The remainder had elevation of the blood sugar.

Blood sugar values of 170 mgm. per 100 cc. or higher were noted in 25 subjects (0.5 per cent). Of the 111 individuals subjected to the glucose tolerance test, eighteen exhibited abnormal curves or 3.6 per cent of the total. Of the eighteen with abnormal curves, ten (2 per cent) definitely had diabetes. The remaining eight (1.4 per cent) were classified as potential diabetics. Of the eighteen with abnormal glucose tolerance curves, six exhibited no glycosuria in the screening test.

The average age of those examined was 39.8 years. The youngest was nineteen and the oldest was 65 years. Of the ten subjects having diabetes mellitus, the ages varied from forty to 65 years. Seven were in the fifth decade of life and the remaining were 55, 60, and 65 years of age. In the group of eight with potential diabetes, the ages were 33, 37, 43, 45, 47, 50, 51, and 62 years, respectively.

DISCUSSION

In the Diabetes Detection Drives the number of new cases discovered varied from 0.0 to 14.0 per cent of the cases examined. It is apparent that the criteria have varied. Had our cases been included in many, if not all, of the surveys they would have been overlooked or considered not to have diabetes. If our group of subjects is an indication of the number of cases of diabetes mellitus which will be overlooked in the routine surveys, then the incidence of diabetes will be approximately 2 per cent greater than those discovered by the usual methods of large surveys. In addition, all of our subjects had had from two to twelve thorough examinations of the usual general annual check-up of carbohydrate metabolism. These examinations satisfied the medical examiners of this company that all of these subjects were healthy individuals and the examinations were more carefully conducted than those required by insurance companies for issuance of large policies. In spite of such examinations, 2 per cent of the people were discovered to have diabetes mellitus and another 1.4 per cent had potential diabetes, thus giving a total of 3.4 per cent.

The criteria for the diagnosis of diabetes mellitus have been a much disputed point. If the criteria accepted by Wilkerson and Krall³ had been employed in our study, 25, or 5.0 per cent of our subjects would have been classified as having diabetes. We, however, are

unable to agree that the height of the blood sugar is diagnostic of diabetes and have accepted the height and prolongation of the curve. It is to be noted in Table 1, which gives the curves of our cases diagnosed as diabetes, that in each case the blood sugar was elevated, the curve was prolonged, and they would be classified as diabetes mellitus by any of the different criteria for the diagnosis of diabetes. In Table 2, on the other hand, the eight cases were designated as potential diabetes by our criteria. All eight cases would have been classified as diabetes by the criteria of Joslin⁴ and Wilkerson.³ We did not deem their curves to be definitely diagnostic and therefore classified them within the normal range.

TABLE 1. Sugar tolerance tests showing diabetes in cases in which hyperglycemia was noted in the screening test.

Case number	Blood Sugar mgm. per 100 cc.			
	Fasting	1 hr. after glucose	2 hrs.	3 hrs.
10	118	275	225	182
41	140	280	190	155
114	128	263	272	216
119	186	276	—	227
178	103	212	205	163
255	117	195	216	180
386	130	190	193	133
409	140	240	270	198
441	113	222	224	147
418	153	184	240	370

TABLE 2. Sugar tolerance tests showing potential diabetes in cases where hyperglycemia was noted in screening test.

Case number	Blood Sugar mgm. per 100 cc.			
	Fasting	1 hr. after glucose	2 hrs.	3 hrs.
8	122	232	173	93
68	113	195	148	132
71	110	174	155	98
73	136	212	120	119
197	104	182	130	127
251	112	220	146	69
476	137	202	132	131
343	105	222	155	124

It is of interest that six subjects with abnormal glucose tolerance curves exhibited no glycosuria in the preliminary screening test. Yet, two of these cases, 386 and 441 (Table 1), had definite diabetes and cases 8, 68, 343, and 476 (Table 2), had potential diabetes. If the urine test alone had been employed for screening, two cases or 0.4 per cent would have been missed. In addition, four other cases of potential diabetes or 0.8 per cent would have been overlooked. The total not detected would have been 1.2 per cent, which is greater than those detected in a large number of surveys.

SUMMARY

Five hundred apparently healthy individuals who previously had been examined in detail two to twelve times, were subjected to a screening test for diabetes mellitus.

In this test, the subject followed a known diet for three days, and then ingested 50 gm. of glucose after the standard breakfast. Those individuals who had hyperglycemia (with the blood sugar over 150 mgm. of glucose per 100 cc.) one hour later were subjected to a standard one-dose-three-hour glucose tolerance test. In this manner, the diagnosis of diabetes mellitus

could be made in 2 per cent of the cases, and an additional 1.4 per cent satisfied the criteria for potential diabetes.

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Major Needs in Nutrition

By many indications, this country's major needs in nutrition today are as follows: (1) control of obesity, (2) elucidation of the role of nutrition in the chronic diseases, (3) assessment of nutritional status as a step toward control of borderline deficiencies, (4) means for complete intravenous alimentation and (5) additional knowledge regarding nutrition in the aged, under stress, and in convalescence. Nutritionists in their efforts to meet these needs should emphasize biochemical and clinical studies of nutrition and metabolism.

OBESITY

Obesity is prevalent throughout the world, occurring even in countries where food is scarce and nutritional status low. In America today it is the gravest known effect of malnutrition. Insurance records indicate that a quarter of the adult population is obese—that is, sufficiently overweight to impair health. Mortality for this group, according to estimates by the Metropolitan Life Insurance Company, is well above normal at every age and rises with increasing weight. Obesity is associated with a high mortality from cardiovascular-renal disease, diabetes, childbirth and diseases of the liver and gall bladder.

Deaths from diabetes are more than three times as common in the obese as in persons of average weight, and deaths from cirrhosis of the liver, among men, more than twice as common. The overweight also have an excessive incidence of hernia, urinary impairments, cancer of the endometrium and some forms of arthritis. Among the nation's major nutrition problems, obesity is in one respect unique. Like pellagra, it can be controlled

in the absence of further knowledge of the underlying mechanism. . . .

DIETARY DEFICIENCY DISEASES

Medical science in general, and certainly nutritional science, would be greatly advanced by further knowledge of how the various dietary deficiencies produce their effects. Pellagra, for example, raises many questions that only intensive metabolic studies may be hoped to resolve . . .

Nutrition science, often through use of biochemical technics, has made notable progress against the major chronic diseases. Here, clinical investigation has been particularly fruitful and should be much extended. . . .

BORDERLINE DEFICIENCIES

Further clinical research is strongly indicated in the problem of borderline deficiencies—that is, conditions presenting an indefinite clinical picture, but nevertheless one of suboptimal health. Such deficiencies are suspected to result in loss of vigor, retarded growth, low resistance to infection, tooth decay, abnormal births and other forms of illness and debility. That these conditions are prevalent is unquestionable, but the extent to which malnutrition is responsible is a matter of few facts and much debate. Those facts require supplementation and possibly intensive action.

From *Trends and Needs in Nutrition*, by W. H. Sebrell, Jr., M.D., in The Journal of the American Medical Association, May 2, 1953

ABSTRACTS

Aarseth, Sverre (*Oslo*): DIABETES MELLITUS DUE TO HEAD INJURY WITH CEREBRAL DAMAGE. *Nordisk medicin* 47:485-86, April 10, 1952.

Experimental and clinical research work suggests that diabetes mellitus is a syndrome the primary cause of which may be extrapancreatic in some cases. Theoretically it must therefore be admitted that diabetes mellitus possibly may be caused by trauma to other organs, especially head injuries with damage to the brain. A 20 year old man in good health, with no diabetes in his family, suffered a severe head injury with multiple fractures of the face and skull, contusio cerebri, penetrating wound of an eye, and commotio labyrinthi. The day after the injury he had symptoms of diabetes. Glycosuria and hyperglycemia continued for 11 weeks. Insulin treatment was started 6 weeks after the injury, and the insulin requirement was as high as 52 units per day. Gradually the manifest symptoms of diabetes disappeared, and insulin was discontinued after 5 weeks. His carbohydrate tolerance was still reduced, as shown by several glucose tolerance tests during the observation period of 9 months. In this case the diabetes is presumed to have been caused by the head injury.

Allen, O. P. (*Akron, Ohio*): SYMPTOMS SUGGESTING PRODROMAL STAGE OF DIABETES MELLITUS. *Ohio M. J.* 49:213-15, March 1953.

The author looked for the following features of a prodromal stage of diabetes mellitus: 1. History of hereditary or diabetes mellitus in the immediate family need not always be present. 2. An initiating toxemia or illness, either infectious or traumatic, followed by: A. excessive gain in weight. B. Excessive appetite and eating between meals, at bedtime, or on waking during the night, which relieves the patient of several of the following symptoms: a. hunger, b. weakness, c. nervousness or irritability, d. trembling and/or fluttering

in epigastrium, e. sweating, f. night sweats, g. restlessness at night, h. dull, weak feeling or headache in morning before breakfast. The above symptoms may be present from 1 to 25 years, (average 12 years). 3. Another infectious or toxic period, soon followed by symptoms of diabetes mellitus: A. Loss of weight, B. polyphagia, C. polydipsia, D. polyuria. Of 1207 patients, 55 per cent presented a prodromal stage. In the last 657 cases, the percentage was over 75 per cent.

Baar, S.; and Bull, J. P. (*Birmingham Accident Hosp., Birmingham, England*): LACTOSURIA FROM CUTANEOUS ABSORPTION. *Lancet* 1:978, May 10, 1952.

In the exposure method for the treatment of burns, it is common practice to apply penicillin-lactose powder to the raw areas. Recent studies on the urine of severely burned patients have shown the presence of reducing sugar several days after the initial glycosuria commonly found in severe trauma. Ward tests with Fehling's and Benedict's solutions were strongly positive; with phenylhydrazine, lactosazone was formed. Milk contains 4 to 5 per cent lactose and might cause lactosuria if given in sufficient quantity to overload the lactase of the intestinal juice. The authors do not know of any harmful effect of this absorption and excretion of lactose, though the possibility of renal tubule damage, as has been attributed to sucrose, should perhaps be borne in mind. These findings should, however, remind us of the great absorptive capacity of the large raw areas of burns and perhaps other skin lesions and of the possibility that reducing sugars appearing in the urine may have entered the body by this route.

Bach, I.; Gyulai, E.; and Viranyi, A. (*Municipal Hospital, Budapest, Hungary*): ADRENOCORTICOTROPIC ACTIVITY AND DIABETES IN ACROMEGALY. *Lancet* 2:1136, December 6, 1952.

ABSTRACTS

The authors discuss the coexistence of diabetes and acromegaly in a letter to the editor. They feel that experimental work corroborates their hypothesis that in man overproduction of growth hormone produces diabetes only where the production of ACTH is not suppressed. According to their findings, in most cases of acromegaly production of ACTH is decreased; and this may be one reason why not every patient with acromegaly or gigantism is diabetic.

Bacon, J. S. D.; and Loxley, R. (*Dept. of Biochemistry, Univ. of Sheffield, Sheffield, England*): SEASONAL CHANGES IN THE CARBOHYDRATES OF THE JERUSALEM ARTICHOKE TUBER. *Biochem. J.* 51:208-13, May 1952.

Analyses of dry matter and of the ketose and combined reducing substances in aqueous extracts were made on tubers of the Jerusalem artichoke during the period of June, 1950, to May, 1951. These confirm the occurrence of a change, already noted by several investigators, in carbohydrate composition during the winter months. A change in the positive direction of the optical rotation of extracts has been correlated with an increase in the proportion of carbohydrate components of lower molecular weight estimated by quantitative paper-partition chromatography. The significance of these findings is discussed in relation to the structures previously proposed for the tuber carbohydrates, and a suggestion is made as to the nature of their metabolic interconversion.

Beardwood, Joseph T., Jr.; Tittle, C. Robert; and Packer, Robert M., Jr. (*Philadelphia and Abington, Pa.*): COMPARISON OF DIABETIC CONTROL WITH NPH AND GLOBIN INSULIN; PRELIMINARY REPORT. *J. Michigan M. Soc.* 51:1298-1302, October 1952.

In an attempt to compare the action of globin insulin and NPH insulin, twenty-two patients were studied. It was the authors' experience that there was no appreciable difference in control of the diabetes in the action of these two insulins at the end of the twenty-four-hour period. This is true of patients taking doses of insulin varying from 20 to 100 units daily in a single dose. It would seem that globin and NPH insulin might give approximately the same degree of diabetic control, and the insulin of choice should be determined by the physician's experience and the individual's response.

Bearn, A. G.; Billing, Barbara H.; and Sherlock, Sheila:

(*Dept. of Med., Postgraduate Med. Sch. of London*): THE RESPONSE OF THE LIVER TO INSULIN IN NORMAL SUBJECTS AND IN DIABETES MELLITUS: Hepatic Vein Catheterisation Studies. *Clin. Sc.* 11:151-65, May 1952.

The technic of hepatic vein catheterization has been used to study the effect of insulin on the liver in 15 normal and 35 diabetic subjects. Insulin (0.1 units per kg. intravenously) results in an immediate drop in the output of glucose from the liver in both normal subjects and diabetics. When normal subjects become hypoglycemic, they show an increase in hepatic glucose output, in hepatic blood flow, in venous lactic acid concentration, and in splanchnic oxygen consumption. In diabetic ketosis there is a greater concentration of ketones in the blood from the liver than in the peripheral venous blood. The difference is greatest in those with the greatest ketosis. Insulin (0.1 unit per kg. intravenously) does not appreciably diminish the blood ketone values. Diabetic subjects have a higher fasting splanchnic oxygen consumption than normal subjects. This can in part be related to hepatic ketone production.

Beidleman, Barkley. (*Med. Center Clin., Pensacola, Fla.*): CLINICAL VITAMIN DEFICIENCIES IN PATIENTS WITH DIABETES MELLITUS. *J. Clin. Nutrition* 1:119-23, January 1953.

Clinical vitamin deficiencies in patients with diabetes mellitus occur (a) when patients are given low-calorie and/or low-fat diets without supplementary vitamin therapy and (b) in otherwise well-nourished patients whose diabetes has been poorly controlled for variable periods of time. In the first group, the perifollicular hyperkeratosis and dry skin of avitaminosis A and the peripheral neuritis and mucous membrane changes of avitaminosis B are most frequently encountered. In the second group, hepatic enlargement responding to choline therapy and diabetic neuropathy responding to treatment with vitamin B₁₂ are discussed.

Bicknell, E. A. (*Detroit, Mich.*): THE FAMILY DOCTOR AND DIABETES. *J. Michigan M. Soc.* 51:1317-18, October 1952.

If diabetes is to be discovered early, there is only one who can do it. He is the family doctor. Most cases picked up early are easy problems, both for the patient and the physician. Any capable G. P. can instruct and handle most diabetics. The unruly and brittle can not

be controlled well by anyone. Our specialist friends should be allowed the chance to help them.

Bortz, Donald W. (*Greensburg, Pa.*): DIABETIC NEPHROPATHY. *Pennsylvania M. J.* 55:1115-17, November 1952.

The author stresses his belief that the incidence of diabetic nephropathy, as in other degenerative lesions associated with diabetes, may be greatly lowered by rigid dietary, metabolic, and infectious control of all diabetic patients, young or old.

Cant, Donald; and Lees, Brian. (*Corner Brook, Newfoundland*): ISLET CELL TUMOUR OF THE PANCREAS. *Canadian M. A. J.* 68:60-62, January 1953.

A case of insulin producing islet cell adenoma in which cure was effected by removal of the tumor is reported. Of interest was a five-hour glucose tolerance test made one year after the onset of symptoms and one and one-half years before operation which was interpreted as indicating functional hypoglycemia but in retrospect attention was directed to a fall in blood sugar still showing at the end of the test.

Carbonnell Aguilar, Carlos D. (*Havana*): AN INTERESTING CASE OF DIABETES MELLITUS. *Boletín del Colegio Médico de La Habana* 3:92-94, March 1952.

The author describes the case of a 62 year old patient, who was seen for the first time in diabetic coma, controlled with 450 units of insulin and supportive therapy. Some days later, emergency surgery for acute cholecystitis was necessary. Regular insulin was used during recovery from surgery; then NPH insulin was adopted as routine treatment.

Chitwood, W. R. (*Wytheville, Va.*): THE EFFECTS OF INSULIN HYPOGLYCEMIA ON THE DIABETIC HEART. *Virginia M. Month.* 80:168-70, March 1953.

In diabetes in which heart disease is such a frequent complication, it is of interest to note what effect the use of insulin has on the heart. Although there appears to be a general consensus that the elderly diabetic with coronary disease should be treated with caution, a careful and detailed study of the effects of insulin on the

heart in a large group of elderly diabetics has never been made. It is hoped that more studies will be made in the future concerning this subject.

It has been proven that insulin does not cause coronary constriction, per se. On the contrary, studies reveal that it causes coronary dilatation. However, some feel that the electrocardiographic changes and the clinical anginal symptoms following insulin are actually due to myocardial ischemia caused in an indirect way. It is thought that the low blood sugar causes an outpouring of epinephrine which in turn causes an increased heart rate and output and brings about the myocardial infarction in elderly diabetic patients receiving insulin, as shown by various reports. Thus, it can be generally stated in the treatment of diabetic patients, first, that young diabetics should be controlled closely with insulin, since evidence points to no serious myocardial effects, and second, that those diabetics who do have coronary disease already present should not be allowed sudden changes in blood sugar levels, especially toward hypoglycemia.

Cohn, Clarence; and Kolinsky, Muriel. (*Dept. of Biochem., Med. Res. Inst., Michael Reese Hosp., Chicago, Ill.*): INFLUENCE OF PREVIOUS DIET ON CARBOHYDRATE UTILIZATION BY THE DIAPHRAGMS OF ADRENALECTOMIZED RATS. *Metabolism.* 2:146-52, March 1953.

The glucose uptake in vitro by diaphragms of young, force-fed adrenalectomized rats is less than the uptake by diaphragms of normal animals. In contrast, the diaphragms of adrenal cortical-deficient animals fed ad lib take up more glucose than those of control rats.

De Oya, J. C.; Diaz, C. Jimenez; and Grande, F. (*Univ. of Madrid, Madrid, Spain*): COMBINED EFFECTS OF NEPHRECTOMY AND SMALL DOSES OF ALLOXAN IN THE PRODUCTION OF EXPERIMENTAL DIABETES. *Bulletin of the Institute for Medical Research, University of Madrid* 5:141-46, July-September 1952.

The average dose of 50 to 60 mg. of alloxan per kg. of body weight causes diabetes to appear in some dogs; in others no such condition occurs. In those dogs which had received this dose, nephrectomy gave rise to severe diabetes in cases in which the condition was previously slight; it had no effect whatsoever in nondiabetic animals. These results confirm those previously obtained by other methods and are in favor of the neutralizing,

buffer action of the renal parenchyma on the disturbances of the carbohydrate metabolism regulation.

Dine, Mark S.; and Jackson, Robert L. (*Iowa City, Iowa*): SERIAL SERUM CHOLESTEROL IN CHILDREN WITH DIABETES MELLITUS OF RECENT ONSET. *J. Lab. & Clin. Med.* 40:793, November 1952.

A total of 435 serial serum cholesterol values was determined in 48 children with diabetes mellitus early in the course of their disease. Before insulin therapy was instituted, a larger number of elevated values were observed, but there were many values within the normal range. Marked fluctuations in cholesterol values in individual patients with diabetes mellitus were noted, particularly in the early weeks of treatment. Hydration accounted for a decrease in cholesterol values in five patients. The average cholesterol values increased in the first three weeks of therapy and then gradually decreased to a value below the average for normal children. During the period of home management (maximum two years), the patients who maintained an excellent or good level of control tended to maintain cholesterol values within the normal range. Those children who maintained only a fair to poor level of control during the period of home management continued to show marked fluctuations in cholesterol values. Cholesterol values showed a significant decrease in five patients with mild or severe infection. No correlation was found between the cholesterol values, the insulin dose, and the age or the sex of the patient.

Editorial (*England*): A NEW KIND OF HOSPITAL FOR DIABETICS. *Lancet* 1:35, January 3, 1953.

Joslin's plan for the education of ambulatory diabetics in hospital is discussed. The patients would not be bedfast; on the contrary they would presumably be fit and mobile, more like a class of college students than a group of sick people. Hence, they would not need the ward care of nurses but could very largely be left to their own devices. The hospital, then, could give them meals in a cafeteria and provide them with opportunities to do light housekeeping, such as is the rule in boarding schools and colleges. Not only diabetics, but doctors, medical students, and nurses would be instructed in the prevention of the long-term complications of the disease.

Editorials and Comments (*Chicago, Ill.*): THE STRUCTURE OF INSULIN. *J.A.M.A.* 151:743, February 28, 1953.

Many attempts have been made to elucidate the chemical nature of insulin since its successful preparation some 30 years ago. It was soon found that insulin was a protein and hence was undoubtedly an extremely complex substance from a chemical standpoint. This was substantiated by the finding that insulin had a high molecular weight, characteristic of proteins, and that it contained nearly all of the amino acids found in most proteins, with the rather remarkable exception of tryptophane, methionine, and hydroxyproline. One group of workers at Cambridge University in England found the insulin molecule had four terminal free amino groups, two of which were from glycine and two from phenylalanine. Further studies in which insulin was oxidized also indicated that the molecule contained two identical pairs of peptide chains.

Today, insulin thus appears to be a protein with a basic molecular weight of approximately 12,000 and to be comprised of two pairs of peptide chains joined together by sulfur-to-sulfur linkages from cysteine. One type of peptide chain contains phenylalanine as the N-terminal amino acid and is composed of 30 amino acids of known sequence; the other two peptide chains contain glycine as the N-terminal amino acid and are composed of 21 amino acids of known sequence.

Evans, John D. (*Dept. of Physiol., Cornell Univ. Med. Coll., New York, N. Y.*): ACETOACETATE AND ESTERASE ACTIVITY IN NORMAL RABBIT BONE MARROW IN VITRO. *Am. J. Physiol.* 171:48-54, October 1952.

Under aerobic conditions in vitro, rabbit bone-marrow cells suspended in Ringer's Solution may either utilize or produce acetoacetate. The rate of oxygen consumption is unaffected by addition of acetoacetate. Meanwhile, the low endogenous levels of marrow glucose and lactate remain essentially unchanged. Esterases exist in marrow cells, hydrolyzing aliphatic esters. Ethyl acetoacetate hydrolysis proceeds as rapidly and completely in bone marrow as in liver, kidney, or lung. The evidence from these experiments is consistent with the concept that rabbit marrow cells are able to metabolize fat. Such ability to use depot fat provides under conditions of starvation an alternate energy source for the formation of blood corpuscles and accounts for the maintenance of the blood count during starvation.

ABSTRACTS

Ferrara, Michael A. (Norwich, Conn.): THE TUBERCULOUS DIABETIC PATIENT. *New England J. Med.* 246:55-56, January 10, 1952 (*Abstr. from Pennsylvania M. J.* 55:1134-36, November 1952).

Of 3,178 patients with pulmonary tuberculosis admitted to the Uncles-on-Thames Tuberculosis Hospital from July 1, 1937, to July 1, 1950, 68, or 2.1 per cent, had associated diabetes mellitus. Of the 68 patients, 53 were discharged and 15 are still hospitalized. Of the 53 discharged, 35 are known to be dead; the disease has been arrested in 11 for periods ranging from six months to nine years; 2 are living with active tuberculosis; and 5 are untraceable. Of the 15 patients still hospitalized, the disease of 7 is active, unimproved, and the disease of the remaining 8 is active, improved. The prognosis for the tuberculous patients who have diabetes is graver than that for the tuberculosis patients who do not have diabetes.

Follette, James H.; Valentine, William N.; and Lawrence, John S. (*Dept. of Med., Sch. of Med., Univ. of Calif. Med. Center*): THE BETA GLUCURONIDASE CONTENT OF HUMAN LEUKOCYTES IN HEALTH AND IN DISEASE. *J. Lab. & Clin. Med.* 40:825-40, December 1952.

The B-glucuronidase activity of leukocytes from normal human subjects varies between 22.0 and 35.6, with a mean value of 28.9 (these figures indicate the number of milligrams of phenolphthalein liberated from substrate per hour by 10^{10} leukocytes). Eosinophils seem to contain a substantial amount of B-glucuronidase. One patient with diabetes, osteomyelitis, and 16 per cent eosinophils was found to have a B-glucuronidase activity of 37.8. The authors report their findings in subjects with various hematologic abnormalities associated with various disease states such as leukemia, etc., but are unable to determine the exact metabolic significance of glucuronide hydrolysis.

Foreign Letters (Brazil, S. A.): BLOOD AMYLASE IN ACUTE PANCREATITIS. *J.A.M.A.* 151:660, February 21, 1953.

A study of 61 cases of acute pancreatitis due to hormonal disturbances was made by Prof. Felicio Cintra do Prado and Dr. Plinio Bove in the Hospital das Clinicas of the University of Sao Paulo. The authors drew the following conclusions from their research: 1. The amylase test of the blood had a conclusive signifi-

cance in the diagnosis of 61 cases of acute pancreatitis. 2. A sudden elevation of serum amylase occurs at the onset of acute pancreatitis. After 48 to 72 hours the amylase tends to fall rapidly, maintaining itself from then on in its normal concentration or a little above that.

Foreign Letters (London): INSULIN NOT A MONOPOLY. *J.A.M.A.* 151:62-63, January 3, 1953.

In December, 1950, the Board of Trade, acting under the terms of the Monopolies and Restrictive Practices (Inquiry and Control) Act, 1948, requested the Monopolies and Restrictive Practices Commission to investigate the question of whether or not the supply of insulin in this country constituted a monopoly under the terms of the act. The Commission's report, which has now been published, is a complete exoneration of the manufacturers from any such accusation; the Commissioners "find that the arrangements now made by the British Insulin Manufacturers, individually and collectively, for the supply of insulin operate and may be expected to operate in the public interest, and we do not recommend that any of them should be discontinued."

Gartner, Samuel (*President, New York Soc. for Clin. Ophth.*): SCLERODERMA WITH RETINOPATHY. *Am. J. Ophth.* 36:120-25, January 1953.

Agatson states that retinopathy occurs with regularity in diseases which affect the renal glomeruli: for example, glomerulonephritis, malignant nephrosclerosis, Kimmelstiel-Wilson syndrome, lupus erythematosus, and periarteritis nodosa. It may occur in dermatomyositis when the kidneys are involved. In other words, many diseases affect renal and retinal capillaries at the same time.

Harris, Laurence V. D.; Albrink, Margaret J.; Van Eck, Willem F.; Man, Evelyn B.; and Peters, John P. (*Dept. of Int. Med., Yale Univ. Sch. of Med., and Med. Service of the New Haven Hosp., New Haven, Conn.*): SERUM LIPIDS IN DIABETIC ACIDOSIS. *Metabolism* 2:120-32, March 1953.

The serum lipids of 15 patients with diabetes have been measured at the height of acidosis and at intervals during treatment. The hyperlipemia of diabetic acidosis

involves all fractions of the lipids to varying degrees, but especially neutral fat. The nature of the disturbance of lipid patterns suggests that hemoconcentration plays an important part in the production of the hyperlipemia as a whole. In addition, there is an accession to the plasma of other lipids. These appear largely in a free state and are responsible for the lactescence of the serum.

Hinkle, Lawrence E., Jr.; and Wolf, Stewart (*Cornell Univ. Med. Coll., New York, N. Y.*): A SUMMARY OF EXPERIMENTAL EVIDENCE RELATING LIFE STRESS TO DIABETES MELLITUS. *J. Mt. Sinai Hosp.* 19:537-70, November-December 1952.

Experimental evidence indicates that stimuli arising out of the life experience of the individual which are either consciously or unconsciously interpreted by him as having important relevance to his security may produce, in both diabetic and nondiabetic patients, fluctuations in the level of ketone bodies and glucose in the venous blood. The magnitude of these changes is much greater in diabetic persons, and if great enough and of long enough duration, they lead to ketosis and hyperglycemia in some cases and to hypoglycemia in others, without the necessary intervention of other factors such as intercurrent illness, changes in physical activity, or alteration of insulin or food intake. Similar stimuli may lead to important changes in the amount of urine excreted by both diabetic and nondiabetic persons. The occurrence of diuresis in a diabetic person under environmental stress may be associated with a massive loss of glucose and electrolytes which is an important factor in the development of dehydration and coma. The life histories of persons with diabetes mellitus and the observation of their responses to events and situations in their daily lives are consistent with the concept that life experiences are of great importance in the onset and course of the disease.

Hirsch, Edwin F.; Phibbs, Brendan P.; and Carbonaro, Lynn (*St. Luke's Hosp. and Dept. of Path., Univ. of Chicago, Chicago, Ill.*): PARALLEL RELATION OF HYPERGLYCEMIA AND HYPERLIPEMIA (ESTERIFIED FATTY ACIDS) IN DIABETES. *A.M.A. Arch. Int. Med.* 91:106-17, January 1953.

The intensity of hyperlipemia in the human diabetic seems to approximate the severity of the hyperglycemia.

The triglyceride fraction of the blood lipids is increased the most and the cholesterol and the phosphatides slightly or not at all. When the hyperglycemic diabetic becomes normoglycemic through diet or insulin or both, the esterified fatty acids of the blood return to the high-normal range. During a fat tolerance test the esterified fatty acids of the blood are much higher in the hyperglycemic diabetic than when he is normoglycemic. The demonstration of an apparently proportional hyperlipemia in a hyperglycemic diabetic emphasizes a control of the lipid content of the blood by maintenance of the blood sugar of diabetic patients at normal levels. According to current views on the role of the lipids in the evolution of atherosclerosis, the maintenance of the blood lipids in diabetics at or near the high-normal range is significant in delaying degenerative vascular disorders.

Hurd, James B. (*Chicago, Ill.*): THE IMPLICATIONS OF DIABETES MELLITUS COMPLICATED BY PREGNANCY. *J. Michigan M. Soc.* 51:1309-13, October 1952.

Today, the pregnant diabetic faces risks of fetal loss obviously far greater than those of her nondiabetic sister. The etiology of this increased fetal loss is not clearly understood. It is certain that it is not due to any single factor. Many things contribute: vascular and renal damage, hormone imbalance, metabolic derangement, and possibly genetic weakness. Much investigation is yet to be done to clarify the etiology of, and subsequently develop corrective therapy for, these deficiencies. An extensive and coordinated program carried out by many investigators is essential. Rigid standards and classifications must be set up to evaluate properly the various theories as to etiology and therapy of this problem.

Ingle, Dwight J.; and Meeks, Robert C. (*Res. Labs., The Upjohn Co., Kalamazoo, Mich.*): SUPPRESSION OF GLYCOSURIA DURING ADMINISTRATION OF LARGE DOSES OF ASPIRIN TO FORCE-FED PARTIALLY DEPANCREATOMIZED RATS. *Am. J. Physiol.* 171:600-03, December 1952.

Aspirin, administered subcutaneously at a weekly dose level of 40, 80, and 160 mg. per day to partially depancreatized male rats force-fed a medium carbohydrate diet, produced a marked suppression of glycosuria, with the degree of suppression proportional to

the size of the dose. Amelioration of the glycosuria was accompanied by reduction in hyperglycemia but not by decrease in urinary N.P.N. The mechanism of this action by aspirin is unknown; it cannot be explained as a nonspecific effect of a toxic compound.

Jackson, Robert L. (*Department of Pediatrics, State Univ. of Iowa, Iowa City, Iowa*): THE FUTURE OF THE YOUNG DIABETIC. J. Iowa M. Soc. 43:175-76, May 1953.

The author reviews some of the problems encountered in the management of juvenile diabetes mellitus. Present-day methods have failed to prevent the development of chronic degenerative vascular changes late in the course of the disease. It is stressed that, to maintain control of his disease, the diabetic patient early in the course of his disease must establish habits of living which provide regularity in food intake, physical activity and rest, and avoid emotional crises. The prognosis of the disease is much more dependent upon good environmental care of the child than on variation in severity of the disease. Until more knowledge concerning the pathologic physiology of the disease is available, good control offers the best means of delaying or averting degenerative changes. An optimistic, rather than a pessimistic, outlook is warranted.

Kern, Arthur R. (*Providence, R. I.*): CUTANEOUS MANIFESTATIONS OF DIABETES MELLITUS. Rhode Island M. J. 36:198-200, April 1953.

The cutaneous manifestations of diabetes mellitus are described and the theories concerning the relationship between the two briefly discussed. Such skin changes may occur in those patients with frank diabetes, those with latent diabetes (normal blood sugar but abnormal response to the glucose tolerance test), and those with the condition described by Urbach as skin diabetes.

Koref, O.; and Errazuriz, O. (*Laboratorio de Fisiopatologia, Universidad Catolica de Chile, Santiago, Chile*): QUANTITATIVE VARIATIONS OF THE NEUTRAL 17-KETOSTEROIDS IN ALLOXAN-DIABETIC RABBITS. Acta Physiologica Latinoamericana 2:84-91, 1952.

Excretion of 17-ketosteroids in the urine was, in 6 normal male rabbits, 0.931 ± 0.108 mg. in 24 hours.

Excretion in 8 normal female rabbits was 0.596 ± 0.026 mg. in 24 hours. Thirteen animals were injected with alloxan, and one animal was given alloxantine. Those animals that were rendered diabetic presented a sharp rise in urinary 17-ketosteroids during the first 24 to 48 hours after injection. This increase was followed by a sudden decrease which was maintained while the metabolic diabetic alteration was present. During the course of a mild transitory diabetes, the values of urinary 17-ketosteroids tended to become normal as soon as the metabolic diabetic disturbance was over. Insulin, when improving diabetic symptoms, also caused an increase of urinary 17-ketosteroids. The evolutionary course in the excretion of 17-ketosteroids in rabbits under the influence of alloxan is discussed from the point of view of Selye's concept of the alarm reaction and the general adaptation syndrome.

Levy, Barnet; and Rugh, Roberts (*Dept. of Dentistry and the Radiol. Res. Lab., Columbia Univ. Coll. of Physicians and Surgeons, New York City*): HEPATIC GLYCOGEN IN ACUTE RADIATION DEATH. Proc. Soc. Exper. Biol. & Med. 82:223-25, February 1953.

In both warm-blooded animals (hamsters, Swiss albino mice) and in cold-blooded amphibia (salamanders), the liver responds to acute x-radiation by a drastic depletion in liver glycogen as determined both by histochemical and microchemical tests.

Lewis, Lena A.; Green, Arda Alden; and Page, Irvine H. (*Res. Div. of the Cleveland Clin. Foundation and the Frank E. Bunts Educational Inst., Cleveland, Ohio*): ULTRACENTRIFUGE LIPOPROTEIN PATTERN OF SERUM OF NORMAL, HYPERTENSIVE AND HYPOTHYROID ANIMALS. Am. J. Physiol. 171:391-400, November 1952.

The serum lipoprotein pattern of normal chickens, guinea pigs, rats, rabbits, opossums, monkeys, human beings, cats, and dogs was determined at a density of 1.21 and 1.063 in the analytical ultracentrifuge. All serums examined at a density of 1.21 except that of the guinea pig contained lipoproteins with flotation rates from S 1 to 15. Cat and dog serums contained no lipoproteins with a rate faster than 23. Those up to the S 30 class were present in rat, opossum, sheep, monkey, and some human serums. Lastly, the 35 or

greater classes characterize guinea pig, chicken, rabbit, and some monkey and human serums. Lipoproteins with flotation rates of S_{1-15} have an electrophoretic mobility of α_1 -globulin, the 20 to 25 class of α_2 -globulin, and the 25 to 40 class of β_1 -globulin.

The concentration of the lipoproteins varied greatly in different species. Those of the S_{1-15} class in cat, dog, opossum, and monkey serums were greater than 200 mg./100 ml. They were about 150 mg./100 ml. in human serums, about 100 mg. in rabbit and rat serums, and about 40 mg. in sheep serums. The 15 to 40 classes in rat serums were of the order of 12 mg.; rabbit, sheep, opossum, cat, and dog, 50 mg./100 ml.; human and monkey greater than 200 mg./100 ml. Arterial hypertension following buffer nerve section in dogs resulted in little or no change in the lipoprotein pattern. The pattern of experimental renal hypertensive dogs showed increased concentration of the $S_{1.21-20-30}$, which frequently appeared as a double peak. The appearance of increased concentrations of α_2 -lipoprotein (S_{23}) and an increase in γ -globulin differentiated experimental renal from neurogenic hypertension. Administration of diets high in cholesterol to dogs and rats with thyroid glands inactivated by treatment with radioactive iodine resulted in greatly increased concentration of lipoproteins, with flotation rates greater than S_{23} . This condition was correctable by feeding desiccated thyroid.

It is probable that serum lipoprotein may be an important factor in determining the differences in susceptibility to atheroma of different species and different individuals. Those with large amounts with flotation rates of S_{35} or faster are most susceptible.

Lockwood, Bruce C. (*Detroit, Mich.*): MILESTONES IN OUR KNOWLEDGE OF DIABETES MELLITUS. *J. Michigan M. Soc.* 51:1295-97, October 1952.

History shows that progress and regress in our knowledge of diabetes, as well as of medicine and science in general, have been concomitant with political and economic stability or instability in the various countries. History also shows that much which appears to be new may be old things rediscovered and refurbished. The dieteric treatment of diabetes has been cyclic since 1800. Our knowledge of the biochemistry and pathophysiology of diabetes has made great advances since the isolation of insulin in 1921. The most fertile fields for future investigation lie in the study of the hormonal

control of enzymatic tissue processes and the behavior and fate of radioactive tagged nutritional components.

Lundbaek, Knud; and Petersen, V. Posborg (*Med. Univ. Clin. Municipal Hosp., Aarhus, Denmark*): LIPID COMPOSITION OF DIABETIC AND NONDIABETIC CORONARY ARTERIES. *Acta medica scandinavica* 144:354-59, January 31, 1953.

Chemical analysis of coronary arteries with pronounced fatty infiltration and calcifications from nondiabetics and patients with diabetes mellitus of long standing showed differences suggesting a specific lipid composition of the arteries in "long-term diabetes." The calcium content was lower in the arteries from diabetics. The cholesterol and total phospholipid content showed no significant difference. The proportions of the phospholipid constituents were different in the two groups, the cephalin content being higher and the lecithin content probably lower, in the arteries from diabetic patients than in those from nondiabetic patients. This result, together with certain clinical considerations, indicates that there should not be a facile nosological labelling of vascular disease in diabetes mellitus as "atherosclerosis."

Mayer, J.; and Silides, Demetria N. (*Dept. of Nutrition, Harvard Sch. of Pub. Health, Boston, Mass.*): A QUANTITATIVE METHOD OF DETERMINATION OF THE DIABETOGENIC ACTIVITY OF GROWTH HORMONE PREPARATIONS. *Endocrinology* 52:54-56, January 1953.

A new method for the determination of the diabetogenic activity of growth hormone preparations, making use of the trophic effect of growth hormone on the blood glucose of hereditary obese-hyperglycemic mice, is presented. The method is rapid and can be used with hormones prepared by different methods, even in the presence of other pituitary contaminants.

Medical Literature Abstracts (*Bologna*): SYNDROMES FOLLOWING GASTRIC RESECTION. *J.A.M.A.* 151:773, February 28, 1953 [*Abstr. from Archivio italiano di chirurgia*].

In a follow-up study of 50 cases of gastric resection the late postprandial syndrome, with accelerated digestion and hypoglycemia, was not found in any.

Neubauer, R. A.; and Sindoni, Anthony. (*Metabolic Clin., Philadelphia Gen. Hosp., Philadelphia, Pa.*): COMBINED ELECTROLYTE THERAPY IN A CASE OF KIMMELSTIEL-WILSON'S DISEASE. *J. Philadelphia Gen. Hosp.* 4:23-29, March 1953.

A series of 23 cases of apparently terminal renal failure have been studied using a different electrolyte approach. These cases consist of nearly all types of chronic renal disease, and the treatment included a combined electrolyte regime. Specifically, this consisted of daily administration either intravenously or orally of 160-300 mEq. of sodium lactate one or one-half molar; small doses of potassium as acetate or chloride (20-40 mEq.); and calcium as lactate or gluconate (4-8 gm.). When the calcium was given orally, it was made up in a 10 per cent solution of Amphojel. With this type of approach certain chemical and clinical changes were noted. All cases showed definite improvement, even dramatic at times. In all cases it was felt that life was prolonged. Chemically there was a rapid drop in the blood urea nitrogen and frequently an overcorrection of the CO_2 combining power (up to 55 mEq./L.), with the expected associated fall in the extracellular chloride level (low of 65 mEq./L.).

A case of Kimmelstiel-Wilson's disease with far-advanced cardiac and renal failure was treated with large doses of hypertonic sodium lactate. The clinical and chemical response was interesting in that the patient became edema-free and alert. Insulin requirements were reduced tremendously, and obvious alterations to the metabolic pathways for carbohydrate utilization occurred. With sodium lactate this patient was able to excrete an equiosmotic urine for sodium. Potassium was administered in spite of uremia, and it was felt that this, along with calcium, also was beneficial. This type of therapy is of use in certain cases of cardiorenal failure, but the indications and contraindications are not yet known. Obviously, there are many inherent dangers, and this form of treatment must be used only under carefully controlled circumstances.

Nichols, George, Jr.; and Nichols, Nancy (*George F. Baker Clin., New England Deaconess Hosp., Boston, Mass.*): ELECTROLYTE EQUILIBRIA IN ERYTHROCYTES DURING DIABETIC ACIDOSIS. *J. Clin. Investigation* 32:113-20, February 1953.

Values for plasma and erythrocyte sodium, potassium, and water in 9 cases during diabetic acidosis and

recovery are reported. For comparison, values in 21 normal subjects are presented.

On admission in diabetic acidosis, plasma-base concentration was normal and plasma water was decreased. Erythrocyte sodium and potassium concentrations were decreased while the water content was normal. Following therapy with insulin and 0.85 per cent sodium chloride solution, the patients showed rapid clinical improvement with return of plasma pH, bicarbonate, and water to normal. Undesirable side-effects of therapy were occasional hypernatremia, the constant occurrence of transient hyperchloremia and hypokalemia persisting for several days. With treatment, the erythrocytes lost no further potassium but did lose both water and sodium. Sodium was reaccumulated in the cells more rapidly than potassium or water. In most cases both cell water and potassium were lower than normal at the time of discharge from the hospital. The mechanism of these changes is discussed. There is a parallelism between water and base shifts in the erythrocytes and in the total cell mass during recovery from diabetic acidosis.

Pocock, Dean S.; and Dickens, Janet (*Veterans Adm. Hosp., California, and Albert Einstein Med. Center, Northern Division*): PARAMYLOIDOSIS WITH DIABETES MELLITUS AND GASTROINTESTINAL HEMORRHAGE. *New England J. Med.* 248:359-63, February 26, 1953.

The authors report a case of primary amyloidosis with diabetes mellitus. This patient clinically showed diabetes mellitus, hepatomegaly, and gastrointestinal hemorrhage, the last causing death. The diabetes was probably the result of extensive replacement of the pancreas by amyloid that was calcified. Although the disease was of the primary type, there was extensive parenchymatous involvement of the liver, pancreas, spleen, and kidneys.

Queries and Minor Notes. (*Texas*): FAT ATROPHY FOLLOWING INSULIN INJECTIONS. *J.A.M.A.* 152:376, May 23, 1953.

Atrophy of subcutaneous fat has been shown to occur in susceptible persons irrespective of the type and pH of the insulin used or the site of injection. It is relatively common. In one large series of diabetic patients, it was found to occur in 44 per cent of those under age 20 and in about 15 per cent of those 20 years of

age or older. In patients under 20, atrophies were only slightly commoner in females than in males, whereas in those 20 years of age and over, the incidence among females was almost seven times as great as among males. Although at present no certain protection from atrophies may be promised, the following suggestions to patients may help: 1. Deposit the insulin beneath or at least in the lower layers of the subcutaneous fat and not superficially. 2. Constantly shift the site of injection so that no one area of 2 cm. in diameter receives insulin oftener than every three or four weeks. 3. If known to be susceptible to atrophies, avoid the arms and legs for injections, and use those parts of the body not exposed to public view, such as the abdominal wall, flanks, and buttocks. As for regeneration of fatty tissue, in many patients the fat will be restored over months or years if the areas of atrophy are avoided for future injections.

Queries and Minor Notes. (*Texas*): TYPES OF HYPERGLYCEMIA. J.A.M.A. 152:376, May 23, 1953.

Following the administration of glucose to a normal subject, the serum phosphorus level falls, presumably reflecting withdrawal of this element for use in the phosphorylation process. This decrease in phosphorus does not take place in the depancreatized animal or in the person with severe diabetes. During a glucose tolerance test, patients with mild diabetes may exhibit a fall in blood phosphorus similar to that seen in normal persons, so that the test is not useful for diagnosis in the borderline situations. Regarding the fall in the blood phosphorus level as an index of peripheral utilization of glucose, some have attempted on this basis to differentiate between true diabetes mellitus and so-called "liver diabetes," in which hepatic dysfunction is considered responsible for the hyperglycemia and glycosuria observed.

Reed, John A. (*Washington, D. C.*): DEVELOPMENTS IN DIABETES DETECTION. Postgrad. Med. 12:489-90, November 1952.

The present status of diabetes detection, including Diabetes Week, is discussed.

Repert, R. Winston. (*Durango, Colo.*): BREAST CARCINOMA STUDY: RELATION TO THYROID DISEASE AND

DIABETES. J. Michigan M. Soc. 51:1315-16, October 1952.

The incidence of thyroid disease is ten times as great and the incidence of diabetes mellitus is eight times as great in women with breast carcinoma than in women of comparable ages in the general population.

Robinson, Charles G.; and Walker, Richard P. (*Rudner Clin., Memphis, Tenn.*): THE TREATMENT OF DIABETES BY THE GENERAL PRACTITIONER. Mississippi Doctor 30:288-91, February 1953.

In addition to specific therapy, the patient with diabetes needs to cultivate an optimistic attitude toward his disease. Many of these individuals are prone to develop a morbid mental outlook. If the patient is a child, undue attention to his condition may lead to behavior problems. By encouraging the patient at every opportunity, the physician can go far toward overcoming such tendencies by explaining to the patient and his family the nature of the disease and the reasons for the treatment, without too much insistence upon the exact performance of minute details of the diet. The patient will then be more likely to consider the goal of treatment in its simplest terms, i.e., that he may enjoy a long and reasonably normal life, and will thus cooperate best in the treatment, with the most fortunate results.

Rodriguez, R. R. THE INFLUENCE OF SEXUAL GLANDS IN EXPERIMENTAL DIABETES. Acta Physiologica Latino-americana 1:226, 1951. (Abstracted from Abstract in Revista de la Asociación médica argentina 66:66, February-March 1952).

Foglia observed a greater incidence of diabetes in male rats than in female rats submitted to an almost total pancreatectomy. The author, belonging to the same school, found that in six months with operated animals there were 89 per cent diabetics among the males and 27 per cent among the females. The difference in behavior neither depends upon greater ingestion of food by the males nor is modified with forced nourishment. Castration has a certain protecting effect in the male and accentuates a great deal the frequency of development of diabetes in the female partially pancreatectomized. The author has observed the protector effect against the appearance of diabetes: dienestrol, estrone, estradiol (benzoate), stilbestrol, ethinylestradiol, ethinyl-

testosterone, and cholesterol (500 micrograms per day). On the contrary, testosterone (propionate) and methyltestosterone favored the appearance of diabetes. Progesterone and desoxicorticosterone did not have any effect. Concerning the mechanism of this protector action of estrogens, the histologic observations of the islands of the remaining pancreas in the treated animals and the action of the implantation of normal animals, which shows in both cases hyperplasia of the pancreatic islands, indicates a direct action of the estrogens on the endocrine system of the pancreas.

Ronchese, Francesco; and Kern, Arthur B. (*Dept. of Dermatology, Rhode Island Hosp., Providence, R. I.*): KAPOSI'S SARCOMA AND DIABETES MELLITUS. *A.M.A. Arch. Dermat. & Syph.* 67:95-96, January 1953.

Laboratory tests on a series of 11 patients with Kaposi's sarcoma have failed to demonstrate the presence of diabetes mellitus. It is suggested that the high incidence of diabetes in the cases reported by Hurlbut and Lincoln may have been in part the result of an abnormal proportion of Jewish patients in their series.

Saka, M. Osman. (*Dept. of Physio-Path., Univ. of Istanbul, Istanbul, Turkey*): HYPERGLYCEMIC-GLYCOGENOLYTIC FACTOR IN DIABETIC MAN AND ALLOXAN-DIABETIC ANIMALS. *Am. J. Physiol.* 171:401-06, November 1952.

In this study, a hyperglycemic and glycogenolytic factor was isolated from the urines of a diabetic man and alloxan-diabetic rats and rabbits. The presence of this active substance was demonstrated in the blood of alloxan-treated animals and diabetic human subjects. The activity of the hyperglycemic and glycogenolytic factor isolated from pancreas and diabetic urine was lost with tryptic digestion, diminished under the action of alkaline, and reversed by the administration of a proper quantity of insulin.

Seaman, Gerald R. (*Carter Physiol. Lab., Univ. of Texas Med. Branch, Galveston, Texas*): ROLE OF THIOCTIC ACID TRANSFER OF ACYL GROUPS. *Proc. Soc. Exper. Biol. & Med.* 82:184-89, February 1953.

When examined in a purified oxidase preparation from the ciliate *Tetrahymena pyriformis* S, thioctic acid is

required for acyl transfer from pyruvate and α -ketoglutarate but not for oxidative activity as measured by reduction of 2,6-dichlorophenolindophenol. The end product of the oxidative phase of pyruvate metabolism is acetate. However, a small amount of acetaldehyde is formed from pyruvate via a side reaction. It is probable that the product of α -ketoglutarate oxidation is succinate and that succinic semialdehyde is formed as a side reaction of this oxidation. Thioctic acid is not required for the acetylation of sulfanilamide from acetyl \sim Co A.

Sherrill, James W.; and Wick, Arne J. (*La Jolla, Calif.*): EFFECT OF PROLONGED ADMINISTRATION OF RADIOACTIVE ZINC⁶⁵ ON THE PANCREAS. *J. Lab. & Clin. Med.* 41:40-42, January 1953.

Radioactive zinc acetate was administered weekly to rats for a six-month period. No diabetic symptoms, such as loss of body weight, glycosuria, or high blood sugar, resulted from the zinc radioactivity.

Smith, Lloyd H., Jr.; Ettinger, Richard H.; and Seligson, David (*Walter Reed Army Med. Center, Washington, D. C.*): A COMPARISON OF THE METABOLISM OF FRUCTOSE AND GLUCOSE IN HEPATIC DISEASE AND DIABETES MELLITUS. *J. Clin. Investigation* 32:273-82, April, 1953.

Experiments were designed to quantitate the rate of utilization of fructose in normal subjects and in patients with the decreased glucose tolerance of parenchymal liver disease and diabetes. The results indicate that fructose is utilized rapidly in normal subjects and at a near normal rate in the presence of marked impairment of glucose tolerance. The serum inorganic phosphate following fructose infusion falls more rapidly than when glucose is infused and returns much earlier toward the fasting level. With glucose infusion, the fall of serum inorganic phosphate is significantly greater in hepatic disease than in diabetes, but the individual variations limit the diagnostic significance of this difference.

The observed differences in rates of disappearance from the blood, the responses of serum inorganic phosphate, and the intermediary compounds suggest a qualitative difference in the metabolic pathways of fructose and glucose.

Soffer, Louis J. (*Mt. Sinai Hosp., New York City*): ADVANCES IN THE DIAGNOSIS OF ENDOCRINE DISEASE. *Bull. New York Acad. Med.* (Second Series) 28:592-605, September 1952.

The response to insulin is a useful adjuvant in the diagnosis of deficient pituitary function. The associated drop in the blood sugar may not be as marked, but its return to normal levels is delayed beyond the 2-hour period. In myxedema there is a delay in the reduction of the blood sugar level by insulin, whereas the return may not be prolonged. When the combined insulin-glucose tolerance test is employed, the "hypoglycemic unresponsiveness" of the patient with hypopituitarism is easily demonstrated, although the curve which is obtained in the patient with primary myxedema resembles that of the normal subject.

Sprague, Randall G.; Kvale, Walter F.; and Priestley, James T. (*Rochester, Minn.*): MANAGEMENT OF CERTAIN HYPERFUNCTIONING LESIONS OF THE ADRENAL CORTEX AND MEDULLA. *J.A.M.A.* 151:629-39, February 21, 1953.

Cushing's syndrome is a distinctive habitus characterized by obesity or an abnormal distribution of fat and wasting of muscles so that the face, neck, and trunk appear obese and the extremities thin and also muscular weakness, hypertension, osteoporosis, amenorrhea or impotence, hirsutism and acne of some degree in the absence of other evidences of virilization, thin skin with distinctive purplish striae and tendency to ecchymosis, and a cervicosoral fat pad. The term should not be applied to obese women with hirsutism and menstrual abnormalities but without unequivocal evidence of adrenal cortical hyperfunction. Some or all of the following conditions should be present: lymphopenia, eosinopenia, alkaline urine, hypochloremic, hypopotassemic alkalosis, and impairment of carbohydrate tolerance as demonstrated by elevated values of the fasting blood sugar or abnormalities of the glucose tolerance test.

If glucose tolerance was abnormal before adrenal resection, it usually improved when other features of Cushing's syndrome regressed. Of the 10 patients who had frank diabetes before operation, 7 had normal values for fasting blood sugar and no glycosuria after operation. In three cases the tests of blood sugar were not made after operation, but there was no glycosuria. Among the patients with abnormal glucose tolerance

curves before operation, there was usually improvement in glucose tolerance after operation.

Spiegelman, Anna R.; and Quigley, Thomas J. (*Metabolic Serv., Sea View Hosp., West New Brighton, Staten Island 14, N. Y.*): ISONICOTINIC ACID HYDRAZIDE IN THE TUBERCULAR DIABETIC. A PRELIMINARY REPORT. *Quart. Bull. Sea View Hosp.* 13:203-04, October 1952.

Ten patients with diabetes who were receiving isonicotinic acid hydrazide therapy for tuberculosis were observed for four months to determine the effect of the drug on the diabetic state. The carbohydrate intake of these patients was increased on an average by 29 grams a day. The insulin requirement rose from an average of 31 units of protomine zinc insulin daily to an average of 43.5 units daily. The average amount of weight gained in the four-month period was 14.3 pounds.

Stetten, DeWitt, Jr. (*Div. of Nutrition and Physiol., the Pub. Health Res. Inst. of the City of New York, Inc.*): RECENT CONTRIBUTIONS TO THE UNDERSTANDING OF EXPERIMENTAL DIABETES. *J.A.M.A.* 1509:71-73, November 8, 1952.

The major primary metabolic defect observed in the animal deprived of its normal source of insulin is an impairment in the utilization of glucose. It should not be supposed, however, that hyperglycemia is, under all conditions, the result primarily of underutilization of glucose. Thus, studies of the rat made hyperglycemic by injections of cortisone showed the rate of glucose production from noncarbohydrate precursors to be six to seven times the normal rate; this probably constituted a major contribution to the glycosuria. The antagonism between cortisone and insulin will thus be seen to be remote and perhaps more apparent than real in that these two agents affect the concentration of glucose in the blood in opposing directions but by different mechanisms.

The exact locus of action of insulin is a question that is being pursued in various laboratories. It is generally agreed not only that the major effect of insulin is on glucose utilization but, further, that insulin must operate early in the sequence of events which initiates glucose utilization.

There is a striking similarity in the biochemical difficulties of starvation on the one hand and diabetes on the other. The starving animal is deprived of its

normal carbohydrate source. The diabetic animal has abundant glucose in its body fluids but, because of some difficulty in the capture or phosphorylation of this glucose by its cells, is not able to utilize it to the greatest advantage. From this point of view, the aptness of the description that has been given to diabetes will be appreciated; namely, that diabetes is "starvation in the midst of plenty."

Thin, Christian; and Robertson, A. (*Dept. of Hygiene and Preventive Med., Royal Dick School of Vet. Studies, Univ. of Edinburgh, Scotland*): THE ESTIMATION OF ACETONE BODIES. *Biochem. J.* 51:218-23, May 1952.

A method has been devised for the estimation of the individual ketone bodies—acetone, acetoacetic acid, β -hydroxybutyric acid, and isopropanol—within the range of 0 to 120 mg. of acetone per 100 ml. The basis of the method is the diffusion of acetone into an alkaline solution of salicylic aldehyde with the production of an orange-red color, the intensity of which is measured in a photoelectric colorimeter. The application of the method to biological materials such as blood, milk, urine, and rumen liquor is described.

Thosteson, George C. (*Detroit, Mich.*): DIABETES DETECTION. *J. Michigan M. Soc.* 51:1306-08, October 1952.

Diabetes mellitus is more prevalent than it has been assumed to be. Group screening will detect the unsuspected case of diabetes. Diabetes can be detected readily if it is kept in mind and looked for in the obese, when there is family history of the disease and when all instances of glycosuria are thoroughly investigated.

Treiber, H. Thomas; and Norton, Harry I. (*St. Mary's Hosp., Rochester, N. Y.*): "MEMBRANOUS" DYSMENORRHEA IN A DIABETIC SIMULATING AN ACUTELY INFLAMED ABDOMEN. *New York State J. Med.* 52:1051-52, April 15, 1952.

A case report.

Valentine, William N.; Follette, James H.; and Lawrence, John S. (*Univ. of California Med. Center, Los*

Angeles, Calif.): THE GLYCOGEN CONTENT OF HUMAN LEUKOCYTES IN HEALTH AND IN VARIOUS DISEASE STATES. *J. Clin. Investigation* 32:251-57, March 1953.

Data are presented on the glycogen content of separated human leukocytes in health and in various disease states. Leukocyte glycogen has been observed to remain relatively unchanged during the postprandial rise in blood sugar, in poorly controlled diabetes mellitus, and in the presence of massive cortisone therapy. Unit cell myeloid leukocyte glycogen tends to be substantially low in chronic myelocytic leukemia and high in polycythemia vera with leukocytosis and/or leukemoid features. It also tends to be substantially above normal in the neutrophilic leukocytosis of infection. The data confirm previous observations that lymphocytes and blast cells are either glycogen-free or extremely poor in glycogen content. The parallelism between unit leukocyte glycogen and alkaline phosphatase activity is discussed.

Van Bruggen, J. T.; Hutchens, T. T.; Claycomb, C. K.; Cathey, W. J.; and West, Edward S. (*Dept. of Biochem., Univ. of Oregon Med. Sch., Portland*): THE EFFECT OF FASTING UPON LIPOGENESIS IN THE INTACT RAT. *J. Biol. Chem.* 196:389-94, May 1952.

The authors investigated the effect of fasting on the ability of the intact male rat to incorporate radioactive carbon (C^{14}) into fatty acid and cholesterol during the first hour following an intraperitoneal tracer dose of C^{14} carboxyl-labeled acetate. The animals fasted 120 hours and lost about 25 per cent body weight and about 75 per cent of their fatty acids. The cholesterol content, however, remained essentially constant. The amount of C^{14} appearing in respired carbon dioxide did not change materially as the fast progressed from 1 to 120 hours. C^{14} appearing in fatty acids and cholesterol decreased to about one-third in this period.

Vere, D. W. (*Med. Unit, London Hosp., London, England*): ESTIMATION OF BLOOD-DEXTROSE BY A RAPID OPHTHALMOSCOPIC METHOD. *Lancet* 2:1017, November 22, 1952.

This note describes a method of estimating the blood dextrose by means of an adapted ophthalmoscope. This method gives an approximation to the blood dextrose

within ± 20 mg. per 100 mg. per 100 ml. The ophthalmoscope is fitted with a device for measuring the intensity of illumination of the retina when a beam of light is shown through the pupil. Originally, the ophthalmoscope was fitted with two polaroid screens, one of which could be rotated over a scale, and a monochromatic light filter to give a sharp cutoff. The red reflex was observed and the analyzer rotated until extinction occurred. An alternative device achieves the same end with neutral graded wedges, but the polarizing ophthalmoscope is more accurate. The unit-area illumination intensity of the retina so measured, with the pupil being used as a stop, is found to vary quantitatively with the blood dextrose. This illumination change is probably due to alteration in the refraction of the eye. This is in keeping with the observation in many patients that vision is impaired when the blood dextrose changes. Experiments are proceeding to investigate the nature of this alteration, which may be due to a physiochemical effect on the lens protein. When suitable corrections for diffusion rate of dextrose, pupil size, and refractive error are applied, a reading of the blood dextrose can be given from the analyzer rotation and a calibration curve, within ± 20 mg. per cent per 100 ml. of the laboratory finding in the Folin-Wu tube. This method has an obvious practical value, since an approximate estimation of the blood dextrose can be made within one minute after the patient's arrival in the diabetic clinic or serial readings can be taken at short intervals at the bedside without samples of blood. The necessary attachments are readily mounted on an ordinary ophthalmoscope.

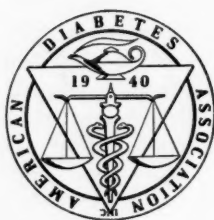
Villee, Claude A. (*Dept. of Biol. Chem., Harvard Med. Sch. and Res. Labs. of the Boston Lying-In Hosp., Boston, Mass.*): REGULATION OF BLOOD GLUCOSE IN THE HUMAN FETUS. *J. Appl. Physiol.* 5:437-44, February 1953.

Tissue slices of placenta and fetal liver were incubated in a Ringer-phosphate medium containing C^{14} -labeled glucose and pyruvate. Analyses show that the glycogen content of the placenta decreases and that of the liver increases as gestation proceeds. Experiments with C^{14} -labeled glucose in the medium showed that the ability

of the placenta to produce glucose decreases with gestation and the ability of the liver to produce glucose increases with time of development. Experiments with other labeled substrates showed that the liver can produce glucose from pyruvate, glycerol, and, to a lesser extent, from acetate. Placenta can produce glucose from pyruvate early in development but not later and can never produce glucose from glycerol or acetate. The placenta, furthermore, has a marked ability to store glycogen early in development. This suggests that the placenta acts to regulate the blood glucose level of the fetus until the fetal liver is able to assume this function.

Volk, Bruno W.; and Lazarus, Sydney S. (*Div. of Labs., Jewish Sanitarium and Hosp. for Chronic Diseases, Brooklyn, N. Y.*): THE INSULIN GLUCOSE TOLERANCE TEST AND THE ABSOLUTE LYMPHOCYTE RESPONSE IN DIABETIC PATIENTS. *Am. J. Digest. Dis.* 19:217-21, July 1952.

The intravenous administration of crystalline insulin (0.1 unit per kg. of body weight) followed 30 minutes later by oral administration of glucose (0.8 gm. per kg.) in 20 nondiabetic individuals produced a characteristic diphasic blood sugar curve, with (1) a low within 30 minutes and a 45-minute level of 20-58 mg. per 100 cc. above the nadir, (2) a return to the fasting value within 90 minutes after the insulin, and (3) a maximum blood sugar level of less than 195 mg. per 100 cc. This was accompanied in all cases by a rise of the absolute lymphocyte count to 41 per cent or more above the fasting value, followed by a secondary decline to at least 27 per cent below the initial level. None of the 27 diabetic patients fulfilled all three criteria for a normal insulin-glucose tolerance test. In addition, the lymphocyte response to the insulin-glucose test differed in each case in some particular from the type of response observed in the normal. It is suggested, therefore, that the insulin-glucose tolerance test either alone or in conjunction with the absolute lymphocyte response might be used as an adjuvant method for the diagnosis of diabetes mellitus in those cases in which the interpretation of the ordinary glucose tolerance test is doubtful.



SERUM LIPIDS AND ATHEROSCLEROSIS

That hyperlipemia may be responsible for atherosclerosis has long been hypothesized on the grounds of what might be termed circumstantial evidence. The first experimental proof of this concept was provided by Anitschkow's¹ demonstration in 1913 that atheroma can be produced in rabbits by feeding cholesterol. In recent years similar lesions have been induced by similar methods in five other species: the dog² (when fed thiouacil in addition to cholesterol), the chicken³, the rat⁴, the hamster^{5a}, and the guinea pig^{5a}.

The use of these observations, however, to defend the argument that atherosclerosis in man originates from excessive levels of circulating lipids is open to several objections. First, it has not been conclusively shown that the experimental lesions are identical with those seen in human arteries, although they are similar. Second, the levels of serum cholesterol which are necessary to produce the disease in animals are far higher than those encountered in most patients. An exception is the finding of Katz⁵, in chickens, that feeding small amounts of cholesterol, with resultant blood levels which are only slightly above normal, still leads to moderately severe atheromatosis of the aorta. Third, the causal relationship between hypercholesterolemia and atherosclerosis which has been so clearly established in other species has not been, and probably cannot be, equally well shown in human beings. For the present, at least, clinical investigators, hampered by the limitations of man as an experimental animal, must be content to determine whether, and how frequently, an association between serum lipids and arterial disease exists, and in so doing must recognize that, while such an association, if sufficiently close, may suggest cause and effect, it does not constitute proof.

Attempts to demonstrate this sort of relationship have taken four lines of approach. It is our purpose critically to review a few of the most significant and representa-

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tive of recent investigations which have been reported in each of these areas.

a. Comparison of Lipid Levels in Living Individuals with and without Arterial Disease

The best indicator of atherosclerosis during life seems to be coronary occlusion. It is generally agreed that nearly all patients dying of myocardial infarction show atheroma of the coronary arteries. Using this criterion, Steiner⁶ made frequent determinations of the serum cholesterol over periods up to two years in fifteen patients with coronary disease proven by clinical and electrocardiographic evidence, and compared these values with those similarly obtained in fifteen normal individuals. A total of 914 determinations of serum cholesterol were made. Values for the former group averaged 355, and for the latter, 254 mg. of cholesterol per 100 ml. The significance of this study lies in the fact that multiple determinations for each subject over many months of time have given it an unusual degree of statistical validity.

Gertler, Garn and Lerman⁷ investigated various lipid fractions of the blood in three groups of men: (a) patients with proven myocardial infarction occurring before the age of 40, (b) miscellaneous normal persons of the same age group as the cardiac patients, and (c) a group of "matched controls," each of whom was selected as being free of coronary disease but closely resembling, with respect to age, weight, body build, national origin and occupation, one of the patients with heart disease. The results (Table 1) show that values for all fractions are highest in the patients, lowest in the miscellaneous controls and intermediate in the "matched controls." It is to be hoped that a careful following of the members of the "matched control" group for evidence of frank coronary disease is being carried out.

It is evident from these and other reports that there is a general trend toward hypercholesterolemia in patients with coronary sclerosis. There are, however, numerous individual exceptions to which insufficient attention has been paid. This is illustrated by the study of Morrison, Hall and Chaney⁸, who determined the serum cholesterol concentration in 200 cases within two days of admission to the hospital for acute myocardial infarction. Of the 75 patients who were under 60 years of age, 68 per cent had concentrations greater than 260 mg. per 100 ml. of blood. Of the 125 patients over 60 years of age, only 48 per cent had abnormally high values. Thus, about one-third of the first group and one-half of the second had normal cholesterol values in the face of clear cut coronary accidents presumably due to atherosclerosis. It must be concluded that at least this kind of vascular disease occurs often in the absence of hypercholesterolemia.

Gofman⁹ has presented data (Table 2) purporting to show that there is a greater difference between normal subjects and patients with coronary disease with respect to the "atherogenic" lipoproteins than with respect to the serum cholesterol. He has reported also that, among patients who have already experienced myocardial infarction, the recurrence rate is 20 per cent per year for those whose S_{γ} 12-20 lipoprotein levels are of the order of 100 mg. per 100 ml., while the recurrence rate is only 6 per cent per year for those whose S_{γ} 12-20 levels are of the order of 50 mg. per 100 ml. That these studies demonstrate some positive relationship between coronary disease and levels of certain serum lipoproteins cannot be denied. Examination of Table 2, however, reveals standard deviations of such magnitude as to suggest that some of the individuals without coronary disease must have had lipoprotein concentrations as high as, or higher than, some of the subjects with coronary disease, and that some of the coronary patients had levels as low as some of the normal persons. As in the case of cholesterol, there appears to be a tendency toward abnormally high levels of the "atherogenic" lipoproteins in patients who have experienced coronary occlusion, but the correlation is by no means complete.

b. Post Mortem Studies of Blood Vessels in Relation to Levels of Serum Lipids

Morrison and Johnson¹⁰ determined the cholesterol content of the first 6 cm. of the anterior descending coronary artery in 11 cases of fatal myocardial infarction and in 14 patients of comparable age who had died of other causes. The cholesterol content

TABLE 1* Serum lipids in myocardial infarction cases, controls and "matched controls"

	Total cholest.	Cholest. esters	Cholest. phosph. lipid
97 Coronary	286.5 \pm 6.6	176.7 \pm 5.5	89.4 \pm 2.0
146 Control	224.4 \pm 3.5	124.6 \pm 2.6	71.4 \pm .9
97 Matched	241.9 \pm 5.5	141.0 \pm 3.9	77.6 \pm 1.3

*From Gertler et al.⁷

TABLE 2* Comparison of serum lipoproteins and cholesterol in coronary disease

	Number of cases	S_{γ} 12-20— S_{γ} 35-100	Mean total serum cholesterol
Normals	253	109 \pm 65	260 \pm 63
41-50 yrs.			
Coronaries	93	191 \pm 93	297 \pm 68
Normals	149	107 \pm 57	274 \pm 65
51-60 yrs.			
Coronaries	126	162 \pm 79	286 \pm 69

*From Gofman et al.⁹

TABLE 3* Relation between cholesterol in vessel wall (coronary) and in serum compared with degree of sclerosis

Deaths	No.	Mg. cholest. per gm. of dried coronary (av.)	Blood cholest. mg.% (av.)	Gross degree of coronary sclerosis (av.)
Coronary	11	20.4	303	3.5
Other	14	5.1	186	1.5

*From Morrison and Johnson¹⁰.

of the vessels was compared with the degree of atherosclerosis as estimated grossly and with the levels of serum cholesterol. As indicated in Table 3, all average values were considerably higher for the patients with infarction than for those without. The individual data, however, show that two of the patients not dying of infarction had Grade 3, and six Grade 2, coronary sclerosis in the presence of normal amounts of cholesterol in the arterial wall and normal concentrations in the serum.

Faber¹¹ measured the cholesterol of the aorta in 26 subjects (all but two were men) ranging in age from 18 to 73 years and attempted to relate these values both to age and to serum cholesterol. The cholesterol content of the aorta was found to rise progressively with age, but it failed to correlate with cholesterol concentrations in the blood. In Figure 1, Faber's data derived from analyses of the aortas have been recalculated and plotted as mg. of cholesterol per gm. of aorta. In the same figure are plotted, not Faber's data on serum cholesterol, which are not numerous enough to be statistically valid, but the average values for serum cholesterol obtained by Keys¹² in a study of 2056 normal subjects, chiefly men, in various age groups.

These data confirm Faber's own in showing a lack of correlation between serum and aortic cholesterol for, although both increase up to the sixth decade, thereafter aortic cholesterol continues to rise while serum cholesterol reaches a peak and then falls with advancing age.

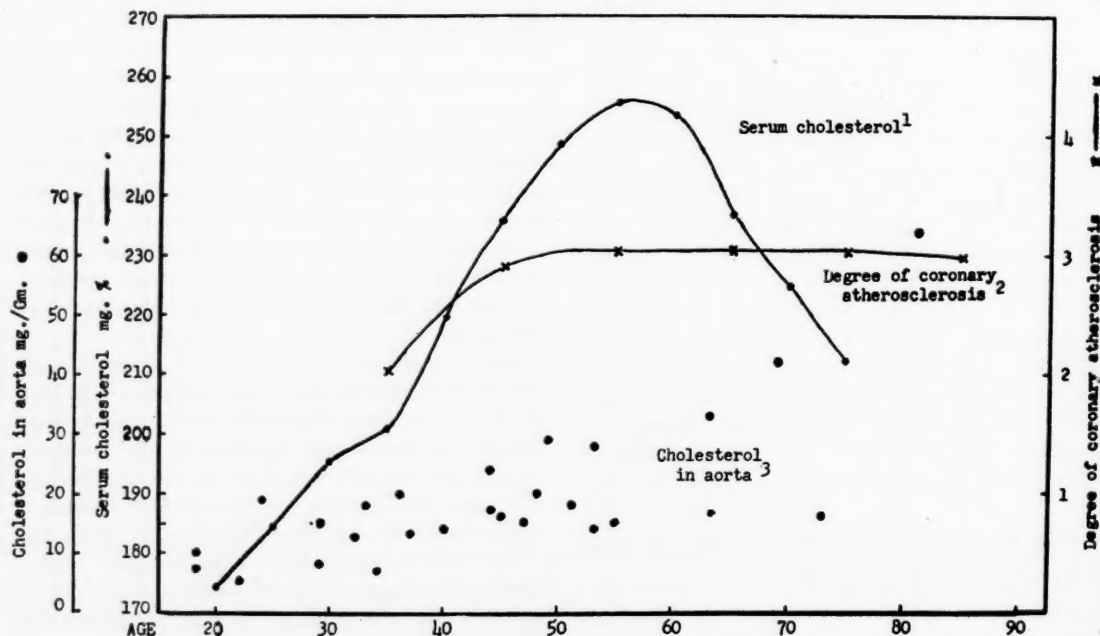
Also in Figure 1 are plotted the results of a study by White, Edwards and Dry¹³ on the relationship of the degree of coronary atherosclerosis with age in men. These investigators made multiple sections of the coronary system of the hearts of one hundred unselected cases in each decade from age 30 through age 89 (six hundred hearts in all) and graded the degree of atherosclerosis on the basis of 1 to 4. As shown in the figure, the severity of coronary sclerosis increases rapidly, along with serum cholesterol, through the fourth and fifth decades and reaches a maximum in the sixth, after which it levels off despite still rising, and later declining, levels of serum cholesterol. It seems likely that coronary atherosclerosis is not entirely a function either of serum cholesterol concentration or of age, whereas aortic sclerosis, as measured by cholesterol content, is related to the latter but not the former. The reasons for the

rise and fall of serum cholesterol with increasing age are not clear.

c. Comparisons of the Dietary Habits of Populations Which Are More Prone, as Opposed to Those Which Are Less Prone to Atherosclerosis

These have generally led to the conclusion that a high fat intake favors, and a low fat intake minimizes, this form of arterial disease. By and large, such investigations have not been sufficiently well documented to provide convincing proof. Furthermore, there has been a dearth of chemical evidence to show that the higher incidence of atherosclerosis reported in peoples subsisting on large amounts of fat is accompanied by increased concentrations of lipids in the blood. Recently Keys¹⁴ and his associates have presented a more complete study of food habits in relation to both the incidence of atherosclerosis, as manifested by coronary heart disease, and levels of serum cholesterol in different European populations. In England, where the incidence of the disease is roughly the same as in the United States, fat constitutes from 35 to 40 per cent

FIGURE 1. Serum cholesterol, cholesterol content of aorta and degree of coronary sclerosis in relation to age



1. Based on data obtained in 2056 normal men (Keys et al¹²).

2. Based on necropsy examination of 600 unselected hearts of normal males (White et al¹³).

3. Based on chemical analyses of aortas from 2 females and 27 males (normal) (Faber¹¹).

of the diet and serum cholesterol tends to be relatively high. By contrast, the poorer classes of Italy, whose diets contain only about 20 per cent fat, have lower levels of serum cholesterol and, it is stated, a much lower incidence of all forms of heart disease including, presumably, coronary sclerosis. In the upper classes of southern Europe, on the other hand, fat intake, serum cholesterol and the estimated frequency of vascular disease are all higher. These differences on dietary fat seem to be reflected in serum cholesterol levels only after age 30. While not supported by adequate vital statistics, these studies, bringing to the problem more quantitative answers than have heretofore been available, bear out the generally accepted association between serum lipids and atherosclerosis. There is little doubt, however, that here, as in other investigations, discrepancies would appear in individual cases were detailed information at hand.

d. Experimental Observations

Such observations in human material, for obvious reasons, have been limited. Space permits mention of only one such study. Evans¹⁵ and others have pulsed the oxalated blood of young normal individuals and of patients with coronary disease, some of them diabetics, against strips of normal human aorta at a pressure of 300/0 mm. of mercury and a rate of 80 pulsations per minute for 72 hours. Seventy-five per cent of strips pulsed with patients' blood showed a well marked deposition of birefringent particles in the vessel wall, closely resembling early spontaneous atheroma, while 82 per cent of strips treated with the blood of normal subjects contained no such particles. Although these ingenious experiments were performed under highly artificial conditions, they do demonstrate a difference between the normal and abnormal bloods in respect to the ease with which their lipid constituents, not chemically identified, were taken up by previously normal aortas.

That long standing diabetes predisposes to premature and severe vascular disease is well known. That diabetes is often accompanied by hyperlipemia has also been known for many years. A relationship between these two facts has been commonly assumed. It is pertinent to ask, however, how frequently elevation of the blood lipids actually occurs in diabetes. For our present purposes, we are not interested in the characteristic lipemia of the untreated diabetic or of the diabetic in acidosis. If the lipids have any significance for vascular disease, it must be by virtue of the levels which obtain in the

treated diabetic over a long period of years. The literature contains surprisingly few reports on this subject, and those that we have are not only conflicting, but are based on analyses made at only a single point in time.

Chaikoff and others¹⁶ compared serum cholesterol, phospholipids and fatty acids in 23 normal children and 26 children with diabetes under good control with diet and insulin. They found no appreciable difference between the two groups, nor did the duration of diabetes or the daily insulin requirement (10 to 68 units) have any relation to the cholesterol levels.

Man and Peters¹⁷ found the serum cholesterol normal or below in 64 per cent of 79 diabetics not suffering from dehydration or acidosis. Of nineteen patients who showed rather marked hypercholesterolemia, sixteen had complicating conditions such as cirrhosis or nephritis which in themselves might have explained the high cholesterol levels. Among the uncomplicated cases the cholesterol did not exceed 304 mg. per cent—certainly not a striking figure.

Pomeranze and Kunkel¹⁸ recently examined 273 diabetics in various clinics in New York City. Almost exactly half had total serum lipids about 750 mg. per cent (the upper limit of normal) while the other half had levels below this.

These data suggest that in children with well controlled diabetes there is little if any increase in blood lipids but that among adults, with diabetes of varying severity and under varying degrees of control, the lipids are elevated in 35 to 50 per cent of the cases.

Respecting lipoproteins in diabetes, Barach and Lowy¹⁹ report the S_{12-20} fraction above 50 mg. per cent in 33 per cent of males and 43 per cent of females. Hanig and Lauffer²⁰ were unable to find any significant difference between normal persons and diabetics. The data of Keiding and associates²¹ would justify a similar conclusion, although they do not state it in so many words. Among the diabetics themselves, S_{12-20} levels tend to be higher in patients under poor control than in those under good control.

The next question is whether the diabetics who do have hyperlipemia are the ones who also have vascular disease. Among the cases studied by the New York group¹⁸, 78 per cent of the patients with hyperlipemia had severe atherosclerosis as shown by electrocardiographic evidence of coronary disease, calcified vessels or retinal arteriosclerosis. Twenty-two per cent were classed as having moderate atherosclerosis or none. On the other hand, of the patients who had normal serum

lipids, about forty per cent had severe atherosclerosis and sixty per cent had a moderate amount or none. We are left, then, with the dilemma of what caused the vascular disease in the forty per cent without hyperlipemia.

Referring again to the lipoproteins, Barach¹⁰ found the S_f 12-20 fraction elevated in 45 per cent of 162 diabetics with vascular calcification. This is not significantly different from the incidence of elevated S_f 12-20 levels in the entire group of diabetics. Essentially the same results were reported by Keiding²¹, with the additional surprising finding that these lipoproteins were distinctly increased in patients with retinopathy. It is not stated how many of the patients with retinopathy also had the Kimmelstiel-Wilson lesion—a condition in which the S_f 12-20 levels are almost uniformly high²².

In the diabetic population, just as in the nondiabetic, it seems clear that while there is some general, over-all association between the level of serum lipids and the occurrence of atherosclerosis, this relationship fails in many individual cases, and that abnormalities of the circulating lipids do not provide a wholly satisfactory answer to the problem.

Should dietary fat and cholesterol be restricted in an effort to prevent vascular disease? In the present state of our knowledge, it would be reasonable to take the position that excessive amounts of these substances should be avoided. On the other hand, the extreme restriction necessary to produce a significant reduction in the lipid constituents of the blood would seem to be unjustified and may indeed be harmful.

SUMMARY

There is no doubt that in certain animals, under certain conditions, the induction of chronic hypercholesterolemia leads to atheromatosis. For the most part, the levels of serum cholesterol in such experiments have been far in excess of those found in patients with naturally occurring atherosclerosis. While the disease in man has a tendency to be associated with higher values for serum cholesterol than are present in normal persons of comparable age, this association is loose and decidedly inconstant, and the differences in cholesterol levels are not striking. Even if they were, it would still remain to be proven that the relationship is one of cause and effect. Studies of the serum lipoproteins do not yet warrant final conclusions. The evidence to date would seem to justify the same comments that have been made concerning cholesterol.

The tendency of the treated diabetic to have increased concentrations of serum cholesterol and lipoproteins is neither so frequent nor so marked as has been commonly supposed. Furthermore, early data indicate that these chemical abnormalities are no greater in diabetics with vascular disease than in those without it. An apparent exception is retinopathy. High levels in intercapillary glomerulosclerosis are more likely a result than a cause of the renal disease.

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SPECIALIZATION AND RESEARCH

In delivering the John Phillips Memorial Lecture before the American College of Physicians in Atlantic City on April 15th, Dr. Charles H. Best prefaced his address with the following cogent remarks on the problems of research and specialization. They should be of

interest to all workers in specialized fields and particularly to readers of **DIABETES**.

"We have obviously passed the point of medical development at which an individual physician can truly qualify as a specialist in all branches of internal medicine. The clinical investigator must concentrate even more than the practicing physician if he is to pin-point his target, clearly visualize the problems, and advance knowledge of his special subject. The physiologist is, of course, also witnessing the division of his "country" into scores of "states," the boundaries of which are fixed by knowledge of technics as well as by scientific interest and capacity. I lecture to advanced students only on carbohydrate and fat metabolism, on blood clotting and thrombosis, and on certain aspects of endocrinology and nutrition, but it requires constant application and effort to keep abreast of the advances in these fields. To plan, direct and do good research you *must* frequently think well ahead of existing knowledge. Occasionally it is known to everyone that a great goal has *not* been reached and the literature may be ignored, but the individual who follows this path more often attains oblivion than fame. When a real advance has been made it is a relatively short time before the weight of interest and ability of other laboratory groups force the originators to share or relinquish leadership. This is as it should be and there will always be hosts of glittering new problems for those who can never be completely happy unless they are venturing into some phase of the unknown. It is more exciting to tackle a problem and, if fortunate, to enjoy for even a brief space the thrill of a new trail, than to develop well-established fields—but the latter course may be much more productive. As long as an investigator can continue to attract young minds and to keep his own open to the myriads of opportunities which lie ahead in research, there is scope—and hope—for him."

Gustave Edouard Laguesse

His Demonstration of the Significance of the Islands of Langerhans

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In the session of the Paris Academy of Medicine, on November 29, 1927, Louis Lapicque¹ summarized the importance of Gustave Edouard Laguesse in the history of the discovery of insulin as follows: "It would require a whole bibliography to enumerate what we owe to Laguesse in the field of the comparative anatomy of the pancreas, first in regard to fish, both selachian and osseous, problems which he solved completely by himself, and also in regard to serpents. But from this point of view his works would have no more than an honorable place in the esteem of scholars and specialists. Laguesse deduced from his observations something, which has made his name worthy to be commemorated forever by biologists and physicians—the concept of the endocrine role of the islands of Langerhans, the development of which led to the practical discovery of insulin, as it appears from the very name given to this physiological medicament^{2, 3}. Of course, Langerhans had noticed them but only as a navigator who notes in his log book an archipelago which happens to lie within the range of his outlook at sea. Laguesse was the explorer who passed on the same route, halted at these "terrae incognitae," went ashore, mapped and surveyed them so thoroughly that it was possible for later scholars to search them for resources for a new therapeutic agent."

In 1925, the Academy of Medicine in Paris awarded the Prix Albert I de Monaco to Gustave Edouard Laguesse and E. Hedon on the proposal of Charles Richet, stressing in this way the merits of these two scientists in the discovery of the internal secretion of the pancreas.

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Laguesse began his histological and anatomic studies on the pancreas in 1889 with a small report on the development of the pancreas in osseous fish⁴. In the session of the Société de Biologie on July 29, 1893, he communicated his observations on the formation of the islands of Langerhans in the pancreas^{5, 6}. Here he presented a summary of this remarkable study which led to the concept of a secretion of a product in the "milieu intérieur" and also to the coining of the term "endocrine secretion." It was the first time that such a function was attributed to the islands of Langerhans. The formations described by various authors were grouped for the first time under this name. In order not to express a premature opinion on their role, Laguesse translated, in a rather picturesque way, the expression used by Langerhans "Zellhäufchen" (a little heap of cells) into "islands of Langerhans," a term which has been universally accepted since that time. In 1906, Laguesse published an important monograph on the anatomy of the pancreas.

When von Mering and Minkowski reported that the total removal of the pancreas in a dog resulted immediately in fatal diabetes, earlier observations were recalled, including the report of Lancereaux of lesions in the pancreas in a man who had diabetes. In the years 1890, 1891 and especially 1892, Hedon confirmed the conclusions of von Mering and Minkowski and reported the important experiment showing the protection against diabetes by a subcutaneous pancreatic graft. Hedon also showed that his subcutaneous graft lost after some time its fistular orifice; the small pancreatic nodule was then only active as a gland of internal secretion.

This strenuous research work, pursued with an admirable scientific logic, was to lead to the discovery of the hypoglycemic hormone of the islands of the pancreas. E. Gley found it in 1905, but failed in preparing ex-

tracts that were regularly active. He wrote a report of his experiments and deposited a sealed package with the Société de Biologie in Paris. At a meeting of this society on December 23, 1922, to commemorate the centenary of the birth of Pasteur, Professor Gley requested that the envelope, deposited by him in February 1905, be opened and read. In this communication, after referring to his earlier researches, in which it was shown that the destruction of the pancreas by the injection of foreign materials into the ducts does not lead to diabetes, Gley stated that it was probable, as indicated by the work of Laguesse, that this was because the islands of Langerhans remained intact. He suggested that the failures of previous investigators to relieve the symptoms of diabetes, by injecting extracts of the entire gland, may have been due to the presence of substances other than the active principle of the islands. He, therefore, prepared extracts from sclerosed remains of pancreas. He found that these decreased the glycosuria of completely depancreatized dogs and alleviated all other diabetic symptoms. Gley's report then indicated his intention to isolate the active antidiabetic principle, to study its mode of action and to see if the extracts could be used on man, either subcutaneously or by mouth. Because of other researches, these problems were laid aside. Previously to depositing this sealed package in 1905, Gley had contributed valuable observations concerning the effects on depancreatized dogs of extracts of the entire pancreas prepared in various ways, and also of defibrinated blood collected from the pancreatic vein. It was because of the negative results obtained by these methods that he proceeded to use degenerated glands. If Gley's action on that day in February, 1905 postponed the maturing of the lifework of Laguesse, he also left to F. G. Banting and C. H. Best the magnificent opportunity to bring insulin into the realm of scientific and therapeutic progress.

Laguesse continued his cytological and histological studies of the pancreas until the end of his career⁷⁻⁹. In February, 1925, as an exchange professor at the Belgian University of Ghent, he gave three lectures on the endocrine gland of the pancreas. The title of the second lecture was "The Endocrine Pancreas in the Embryo and in the Vertebrates." This summary of the numerous research reports on the intimate relations of these obscure cells ("cellules troubles") with the blood vessels has still today a great value as an objective document.

In a recent monograph by Helmut Ferner¹⁰, the embryonic aspect of the endocrine islets of the pancreas is emphasized. When from 1923 to 1931, Max Aron¹¹

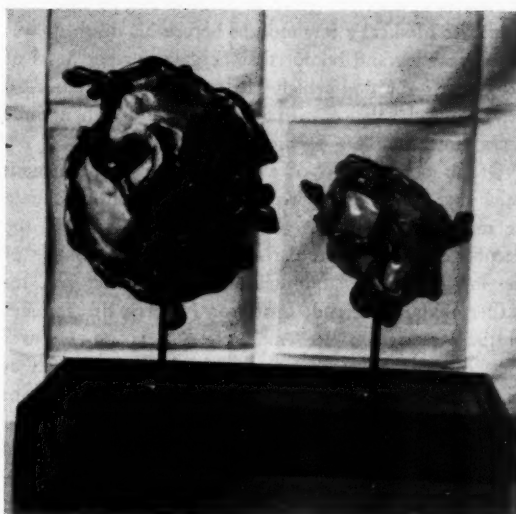


FIGURE 1

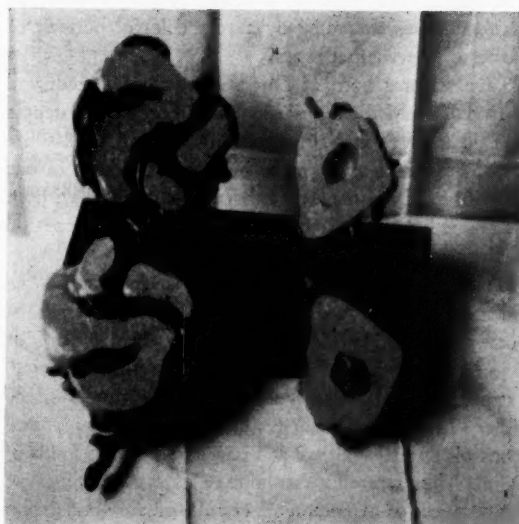


FIGURE 2 External (Figure 1) and cut-away (Figure 2) models of the islets of Langerhans, made by Professor Laguesse about 1905.

took up the study of the correlation of embryonic endocrine glands and the maternal organism, he proposed to give the name of the islets of Langerhans to the adult structures and islets of Laguesse to the embryonic aspects of the endocrine islands. These are the "Mantelinseln" described by Ferner and Stockenius.

In 1927, Laguesse had the pleasure of stressing the meaning of his histological contribution to the discovery

of insulin in a lecture given at Brussels and published in *Bruxelles Médical* a few months before his death. It was with great joy and humor that he gave further news of "Zigomar," the dog which Hedon had kept in normal physiological balance with insulin for more than three years after complete pancreatectomy.

Of his other works of a remarkable and permanent value that do not deal with the pancreas, mention should be made of his studies on the spleen (Thesis of the Faculty of Sciences in Paris) and on the structure of the lungs. An outstanding biologist, Laguesse was, together with his friend, Professor Nicolas, the founder of the Association des Anatomistes in 1899. He was the head of the laboratory of histological research at Lille from 1896 to 1927. Scientifically, the career of Laguesse belongs to the patrimony of the University of Lille. He was succeeded by A. Debeyre¹². At present Professor Morel holds the professorship of histology once held by Laguesse and keeps the many blocks of pancreas, once the material of Laguesse's life work. In the magnificent new medical building of Lille, newly completed, the dean's office is decorated by a very colorful portrait of Laguesse in academic robes.

Laguesse was born at Dijon in 1861. He graduated as Doctor of Medicine in 1885, and received the degree of Doctor of Science in 1890. He devoted all his life to the pursuit of science; the historical evolution of our knowledge of the pancreas cannot be conceived without his research work and that of his students over a period of thirty years.

The father of Laguesse was a physician; he did not practice medicine, but became Professor of Botany at the Medical and Pharmaceutical School of Dijon and Director of the Botanical Gardens. In Dijon, a street is named after Laguesse, but it is in honor of the father. Laguesse remained devoted to Burgundy and spent his annual holidays at Fixin, about 8 km. south of Dijon. After receiving the homage of his colleagues on the occasion of a memorable session of the Association

des Anatomistes in London in 1927, Gustave Edouard Laguesse died at Dijon on November 6, 1927.

Laguesse had no children; but his life was that of a man of science, and he was admired by all his colleagues and honored as a father by his collaborators and students.

ACKNOWLEDGEMENTS

I have to thank Professors Giroud and Verne of the medical Faculty of Paris and the Professors A. Debeyre and Morel of the University of Lille for their obliging help which has enabled me to elaborate this biographical note.

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Freedom and Finance in Research

I view with some uneasiness this trend toward more government support of research. So many people are willing to accept a modern version of the old-time medicine man's sales talk. The medicine man sold his "snake-oil" as a cure-all, for everything from dandruff to bunions. The modern snake-oil peddler tries to sell us the notion that all our ills can be cured with the Federal subsidy panacea. Some Federal support of research is necessary and good, but the snake-oil peddler

of today insists upon more and more government support—of research, of this and that, of practically everything. This condition will surely, if allowed to continue, result in the enslavement of science—and science can thrive only on free soil.

From *Freedom and Finance in Research*, by Roger E. Reid, in *American Scientist*, April, 1953

Recent Statistics on Diabetes

Provisional data for the United States for the entire year 1952 shows that the death rate from diabetes was about 2 per cent less than in 1951 (see Table 1). In the urban population, represented by the experience among Industrial policyholders of the Metropolitan Life Insurance Company, the decline was even greater—8 per cent. The local and State areas from which data are regularly obtained show some deviations from this over-all pattern. For New York State, New York City, Baltimore and Philadelphia there was an increase in the mortality from the disease during 1952. The two Canadian cities, Toronto and Montreal, showed divergent trends. Toronto's death rate dropped appreciably while that for Montreal was up slightly.

In England and Wales, the 1952 death rate showed a sizable decline from 1951. There was a reduction of 10 per cent in the rate both for males and females. For the Administrative County of London the mortality fell 4 per cent in 1952.

The provisional data by regions of the United States, based on the 10 per cent sample of death certificates, showed variations in the direction and degree of change between 1951 and 1952 (see Table 2). The mortality from diabetes was lower in all regions except the Middle Atlantic and the Mountain States. The rate was down most in New England and the South Central section of the country. In the Middle Atlantic area there was a 15 per cent increase. An even larger rise proportionately was recorded in the Mountain States, but the size of the sample for that area is small and the rate is subject to marked fluctuations.

For the first quarter of 1953, the diabetes death rate for the United States, based on the 10 per cent sample, shows a very appreciable increase over the same period a year ago (see Table 1). Increases are recorded not only in all but three of the local areas reporting in this country and Canada but also in London. The primary cause for the rise is the prevalence of moderately severe

epidemic conditions during a part of the period, which is reflected in the rise in the death rate from respiratory disease, in that from all causes, and in that from major chronic diseases particularly. Table 2 also indicates that the rise in mortality was quite general throughout the country. In assessing the different rates of change, the reader is reminded that deviations may, in part, be due to the relatively small number of deaths in the 10 per cent sample for some areas.

Final figures, as shown in Table 3, on diabetes deaths for the United States in 1950 are now available by color and sex. For the country as a whole, the number of deaths ascribed to diabetes in 1950 was 24,419, or about 3 per cent less than in 1949; as against a reduction of 4 per cent in the death rate. The rate among white males was down 3 per cent and that for white females down 6 per cent. In contrast, the rates among nonwhite persons rose 8 per cent for males and 0.5 per cent for the females.

The Demographic Year Book, published by the United Nations, contains a wealth of material on longevity and mortality in various countries. Statistics on diabetes mortality, published in the Year Book for 1952, are abstracted, with some additions from other sources, in Table 4. This table brings somewhat more up-to-date the figures reported in the May-June, 1952 issue of *DIABETES*.¹ The level of the rates are affected by the factors cited there. While the new figures are reported to relate to diabetes deaths classified according to the Fifth Revision of the International List, the principles adopted in connection with the Sixth Revision were already in force in England, Sweden and some other countries. Nevertheless, the table shows that the highest rates continue to prevail in the United States, parts of the British Commonwealth and certain countries of western Europe.

The Eastern Health District of Baltimore has been the scene of a long continued and intensive study of illness among a sample of the families living there. Various aspects of chronic disease have been among the important elements of the study. Consequently, the findings recently published on diabetes² in this small

Submitted by Herbert H. Marks, Chairman, Committee on Statistics. The Committee welcomes suggestion or actual material suitable for these papers from Association members and other readers of the Journal.

RECENT STATISTICS ON DIABETES

TABLE 1 Deaths and Death Rates—1951 and 1952 — and January-March, 1952 and 1953

Area	Death Rates per 100,000				Number of Deaths			
	Jan.-Dec.		Jan.-March		Jan.-Dec.		Jan.-March	
	1952	1951	1953	1952	1952	1951	1953	1952
United States (10% sample)	16.2	16.5	18.9	16.6	2,525	2,528	735	634
Metropolitan Life Ins. Co.								
Industrial Policyholders	14.0	15.2	16.8	13.7	2,589	2,847	760	631
New York State	20.6	20.1	22.8	21.6	3,146	3,024	872	820
New York City	20.3	19.8	23.0	20.7	1,637	1,563	463	416
Maryland, Resident	19.3	20.4	19.3	19.9	473	489	119	121
Baltimore, Resident	22.8	22.7	22.8	26.1	218	216	54	62
Boston, Resident	26.7	29.0	29.0	31.2	216	233	58	62
Philadelphia	26.7	24.2	34.6	31.4	564	506	182	165
Toronto	14.2	17.1	16.4	12.6	95	112	27	21
Montreal	17.7	16.7	19.4	18.5	185	171	51	48
London (Administrative County)	9.2	9.6	11.4	9.5	308	324	96	80
England and Wales								
Total	7.6	8.5		8.8	3,338	3,703		955
Males	5.2	5.8		6.2	1,091	1,219		324
Females	9.8	10.9		11.2	2,247	2,484		631

Note: Rates for the states and cities are based upon local estimates of population. United States data based upon the returns from a 10 per cent sample of death certificates received in vital statistics offices, as published in Current Mortality Analysis, a monthly report of the National Office of Vital Statistics of the U. S. Public Health Service.

TABLE 2 Number of Deaths and Death Rates for Diabetes in Geographic Division; United States Reporting Area for the 10 Per Cent Sample; 1950, 1951 and 1952 and First Three Months of 1951, 1952 and 1953

Geographic Division	Death Rates per 100,000*			Number of Deaths*		
	1952	1951	1950	1952	1951	1950
U. S. reporting area	16.2	16.5	16.6	2,525	2,528	2,501
New England	20.2	24.1	22.5	191	218	206
Middle Atlantic	22.0	19.2	20.5	682	591	627
East North Central	19.2	20.1	20.8	602	623	638
West North Central	17.7	17.9	17.9	256	256	256
South Atlantic	12.5	12.9	14.0	273	279	284
East South Central	10.2	12.0	10.0	120	141	114
West South Central	10.5	12.2	11.0	158	180	162
Mountain	15.4	10.8	8.1	81	56	39
Pacific	11.0	12.5	11.8	162	184	175
January-March						
U. S. reporting area	18.9	16.6	18.1	735	634	682
New England	21.1	20.8	30.1	50	48	70
Middle Atlantic	25.1	22.0	18.1	193	169	136
East North Central	23.3	19.2	24.9	182	149	189
West North Central	20.7	19.0	19.7	74	68	69
South Atlantic	17.1	12.9	15.1	94	70	80
East South Central	11.3	11.6	9.8	32	34	28
West South Central	14.3	10.2	11.6	54	38	42
Mountain	9.6	15.4	12.6	13	20	16
Pacific	11.1	11.1	14.4	43	38	52

*Excludes Armed Forces overseas.

Note: These data from the 10 per cent sample are subject to sampling error. The number of deaths, as given, does not cover the entire United States for each month but is limited by the completeness of the reporting area. The size of the reporting area is indicated by the footnote on page 7 of each monthly issue of the Current Mortality Analysis.

Source: Data furnished by National Office of Vital Statistics of the U. S. Public Health Service.

TABLE 3 Deaths and Death Rates from Diabetes Mellitus by Race and Sex, United States, 1949 and 1950

Sex	Death Rate per 100,000*		Number of Deaths*	
	1950	1949	1950	1949
Total	16.2	16.9	24,419	25,089
White				
Male	12.8	13.2	8,580	8,717
Female	20.0	21.2	13,567	14,158
Nonwhite				
Male	10.0	9.3	768	714
Female	18.7	18.6	1,504	1,500

*Excludes Armed Forces overseas.

Source: National Office of Vital Statistics—Special Reports, National Summaries.

but carefully studied population are of general interest. The observations relate to cases ascertained in a sample population observed from two to five years during June, 1938 to May, 1943. The families living in 34 city blocks were visited at monthly intervals to obtain a record of illness among their members. This record covers a period of five years for families in one-half of this area, and in the remainder for three years where no persons with chronic disease were reported during the period. The investigation was extended to 34 addi-

tional blocks which were canvassed in July, 1941 and families which reported one or more cases of chronic disease were observed until June, 1943. It is not possible to estimate rates of prevalence from the data, but certain of the facts on the diabetics coming under observation are useful. Altogether, there were 89 diabetics among these families, 62 females and 27 males. Two of these cases were lodgers. The further descriptive data excludes them from consideration.

The year of diagnosis was unknown in eight of the 87 family members. Of the cases with known time of diagnosis, approximately half were made during 1938-1943, of which eighteen were new cases. In eleven, or approximately one-seventh of the total, the diagnosis was made before 1930 and the remainder were diagnosed between 1930 and 1937. This distribution, perhaps, gives some indication of a fairly high death rate in earlier years among diabetics in the class from which the sample is drawn, but it is probably influenced more by the increased frequency of discovery of cases as a result of the intensive observation of the families in the study.

Table 5 summarizes the facts on the distribution of the cases according to age at which the first diagnosis

was made. This fact was known in 79 of the cases. In only four cases, all of them males, was the diagnosis made at ages under 35. The median age at diagnosis was about 55. In nearly 30 per cent of the cases the diagnosis was made at ages sixty and over. This proportion was distinctly higher in women than in men.

The disability record of the group is of interest. Of the 87 diabetics, nine were permanently disabled during the entire period of observation and one additional case became disabled during observation. Among the remaining 77 diabetics, the rates of disabling days per 1,000 person days at risk, by sex and age groups, is shown in Table 6. On the whole, the record is a creditable one.

For further interesting details on this carefully observed group of diabetics covering such items as early versus late diagnosis, severity, reported method and degree of control, amount and type of medical attendance, the reader is referred to the original article.

Pre-employment examinations afford a useful opportunity for diabetes detection at the working ages. The experience of the Hawk-Eye Works of the Eastman Kodak Company, reported a few years ago by its Medical Director, Dr. Gordon M. Hemmett, is of particular interest because of the care with which the observations

TABLE 4 Number of Deaths and Death Rates from Diabetes for Selected Countries

Country	Year	Number of Deaths	Death Rate per 100,000
United States	1950	44,790	29.7
Canada (1)	1949	2,749	20.5
Austria	1950	497	7.2
Belgium	1950	1,378	16.0
Denmark (2)	1950	966	22.6
England and Wales	1951	3,703	8.5
Finland	1950	215	5.4
France	1949	3,792	9.1
Germany, Federal Republic	1950	4,544	9.5
Ireland, Republic of	1949	250	8.4
Italy	1950	3,746	8.1
Netherlands	1949		9.3
Norway	1950	469	14.4
Portugal	1951	457	5.3
Scotland (3)	1949	536	10.3
Spain	1950	1,527	5.5
Sweden	1949	508	7.3
Switzerland	1950	573	12.2
Australia (4)	1949	1,473	18.6
New Zealand, excl. Maoris	1949	355	20.1
Colombia	1950	268	2.4
Ceylon	1949	522	7.2
Israel (5)	1949	92	10.2
Japan (6)	1949		2.3
Union of South Africa (7)	1948	259	10.3

(1) Excludes Yukon and Northwest Territories.

(2) Excludes civilian aliens.

(3) Excludes Armed Forces outside country. Rate base includes these.

(4) Excludes full-blooded aborigines. Includes armed forces outside country.

(5) Jewish population.

(6) Japanese nationals in Japan.

(7) Europeans only.

Source: Demographic Year Book—United Nations, 1952.

TABLE 5 Percentage Distribution of Diabetics According to the Age of First Diagnosis, by Sex—Eastern Health District of Baltimore, 1938-1943

Age at First Diagnosis	Both Sexes	Male Percent	Female
All Ages	100.0	100.0	100.0
Under 35	5.1	16.0	0.0
35-39	11.4	12.0	11.1
40-44	11.4	4.0	14.8
45-49	6.3	4.0	7.4
50-54	20.2	24.0	18.5
55-59	16.5	20.0	14.8
60-64	13.9	12.0	14.8
65-69	5.1	4.0	5.6
70-74	7.6	4.0	9.3
75 & over	2.5	0.0	3.7
Total-Known Ages	79	25	54

Source: Simon, K.: Characteristics of diabetes as revealed in a general morbidity study. The Milbank Memorial Fund Quarterly, Vol. 31, No. 1, January 1953.

TABLE 6 Rate of Disabling Days Among Diabetics Who Were at Risk of Disability. By Sex and Age Group—Eastern Health District of Baltimore, 1938-1943

Age Group	Rate per 1,000 Person—Days at Risk		
	Both Sexes	Male	Female
All Ages	21.4	29.6	18.3
Under 45	15.6	16.3	15.1
45-64	13.2	34.5	4.6
65 & over	55.5	20.9	58.3

Source: Same as Table 5.

were made.³ Among 10,167 applicants for employment during 1943-1947, almost equally divided between men and women, 56 were found to have diabetes, or 5.5 per 1,000. In thirty of the cases, or 3.0 per 1,000, the diagnosis was previously known. In 26, or 2.6 per 1,000, the disease was newly discovered. This accords well with other studies which show the known and unknown cases to be approximately equal in frequency. Another point of interest is that 27 cases were found to have renal glycosuria.

A great majority—45 of the 56 diabetics—were males. This probably reflects the higher average age of the male applicants for employment. Of the total, 27 were between ages eighteen and 34, seventeen at ages 35-49 and twelve at ages 50-65. The proportion of

previously undiagnosed cases is somewhat greater at ages over 35 than at the younger ages. From the rough data on the age distribution it appears that the total prevalence in the study varies little by age. This probably reflects certain characteristics of the composition of this group of applicants for employment.

HERBERT H. MARKS

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¹ Dublin, L. I., and Marks, H. H.: Mortality from diabetes throughout the world. *Diabetes* 1:205-17, May-June 1952.

² Simon, K.: Characteristics of diabetes as revealed in a general morbidity study. The Millbank Memorial Fund Quarterly 31:5-23, January 1953.

³ Hemmett, G. M.: Incidence of diabetes mellitus among applicants for employment at an industrial plant. *J. Indust. Hyg. & Toxicol.* 31:261-63, September 1949.

Technics of Weight Control

Whatever may be the primary defect which results in great weight gain, the only way we now have of attacking it is by dietary restriction. And so far as we now know, every case of obesity is amenable to this form of therapy, though the obstacles to success may often be exceedingly difficult to overcome. . . .

There are a few tricks, gleaned from experience, that may be worth noting. For some unknown reason, better results are achieved if the total caloric intake is divided into three even partitions, rather than having the patient eat a tiny breakfast and lunch in order to have a big dinner at night. It is remarkable how many obese persons follow the unbalanced intake method instinctively, and experimental evidence from rats indicates that food eaten all at a sitting tends to greater weight than if the same total quantity is consumed at three or four sittings.

One must watch out for alcohol. Many persons forget that the caloric value of alcohol is 7 calories per cc., so that 3 ounces of whiskey yield 315 calories.

"Appetite killers," such as benzedrine or dexedrine, have been advocated as adjuvants to dietary regimens. They are also used for the emotional lift in relieving depression and to boost morale for dietary maintenance. It has not been our practice to use these drugs (and no collaborating psychiatrist so far has recommended them for any of our patients). In reality they are crutches to lean upon, and it is usually wiser to face and work out the long-term problem squarely. . . .

There is no rationale for restricting either fluid or salt in an obesity regimen unless such is indicated by some complicating cardiac or renal disease. Nor has it ever been clear to me why antidiuretic hormone of the

posterior pituitary is given to help lose weight. Sweating procedures, widely used by boxers and wrestlers to meet certain weight deadlines, obviously have no place in the subject here under discussion. Actually the amount of calories so expended is exceedingly small, and the excess appetite engendered by the procedure usually more than negates its value.

Carefully outlined postural exercises, however, are often of great benefit. Great obesity is almost always accompanied by faulty body mechanics, especially lumbar lordosis with tense back muscles and weak abdominals and glutei. Correction of such postural defects reduces the waistline, promotes erect carriage and gives such a sense of increased well-being and assurance that it is highly recommended whenever feasible. Whether really true or not, I cannot say; but it has seemed to us that, when weight is being lost by dietary means, coincident development of weak muscles of the abdomen and pelvis has seemed to make the fat come off more freely. . . .

Although dietary restriction is the keystone of the weight reduction regimen—at least in the present state of our knowledge—other factors than the prescribed diet, are usually the cause of therapeutic failure. The successful regimen must be planned for the total individual, his emotions, his pocketbook, his palate; and if you are fortunate enough to have the collaboration of a dietitian, a physiotherapist and, if need be, a psychiatrist, your chances of achieving success for the patient will be greatly enhanced.

From *Obesity*, by John Eager Howard, M.D., in the Maryland State Medical Journal, March, 1953

BOOK REVIEWS

EXPERIMENTAL ATHEROSCLEROSIS. By Louis N. Katz, M.D., Director, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Professorial Lecturer in Physiology, University of Chicago, and Jeremiah Stamler, M.D., Research Associate, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago. Cloth. \$9.00. Pp. 360 with 36 illustrations. Charles C. Thomas, Springfield, Illinois. Blackwell Scientific Publications, Ltd., Oxford, England. Ryerson Press, Toronto, 1953.

The authors present a review of clinical, pathological, and biochemical studies of atherosclerosis, listing 1713 references, dealing with such matters as the significance of dietary cholesterol, the large lipoprotein molecules, and the role of hormonal factors and physical forces. Experimental studies, chiefly based on the use of the chick as an experimental animal, are described in detail. Of special interest is the demonstration of the reversibility of atherosclerotic lesions. Strong support is presented for the concept that excess cholesterol or altered cholesterol metabolism is always present in the active stages of human atherosclerosis.

HORMONAL FACTORS IN CARBOHYDRATE METABOLISM, VOLUME VI, Ciba Foundation Colloquia on Endocrinology, edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., assisted by Jesse S. Freeman, M.B., B.S., D.P.H. Cloth. 35s. 350. J. & A. Churchill Ltd., London, England, 1953.

The volume contains papers presented at a conference held in London in the summer of 1952, attended by outstanding leaders in physiologic research. The program,

arranged by Professor F. G. Young of Cambridge, dealt with such matters as the enzyme systems concerned in carbohydrate metabolism, the hormonal control of the interconversion of carbohydrate, protein and fat, the role of the anterior pituitary in the synthesis of fat from carbohydrate, as well as the influence of insulin, the sex hormones and the hormones of the adrenal cortex on carbohydrate metabolism.

The detailed information contained in the papers is supplemented by inclusion of the informal discussion in which the members of the conference actively participated under the guidance of the Chairman, Professor Charles H. Best. The volume will be a valuable source of information for all research workers and for practicing physicians who wish to keep abreast of progress in the study of biochemistry and physiology relating to diabetes.

CONNECTIVE TISSUE: Transactions of the Third Conference, February 14-15, 1952, New York. Edited by Charles Ragan, M.D., Department of Medicine, College of Physicians and Surgeons, Columbia University, New York. Illustrated. Cloth. \$3.50. New York: Josiah Macy, Jr. Foundation. Pp. 166.

The conference was chiefly concerned with fundamental problems in physical chemistry and physiology, relating to connective tissue. The book is a source of information useful to scientists. The interest to the clinician lies solely in the hope that the researches of the active workers in this field will ultimately lead to a better understanding of the so-called collagen diseases and other clinical problems related to connective tissue in the human body.

ORGANIZATION SECTION

Report of the President

Frank N. Allan, M.D. BOSTON

Each year it is customary for the President to present a survey of the affairs of the Association, an analysis of its present needs and an appraisal of future developments. I welcome the opportunity to discuss the thriving state of affairs which now exists.

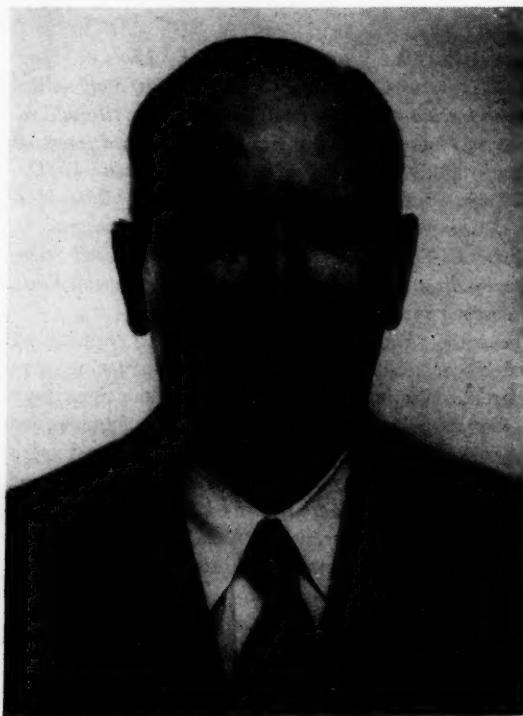
The thirteenth year of the American Diabetes Association has been another year of progress and achievement. There has been a substantial increase in membership; the total number of members is now approaching 2000. This growth reflects a "spontaneous" interest in diabetes by an increasing number of physicians; there has been no membership drive. It is hoped that even more rapid growth will occur in the future; with so many diabetics everywhere, many more doctors should receive the help in caring for them which the Association is eager to provide. A change has now been made in the constitution to simplify the admission of new members. There are now only two requirements—an interest in diabetes, and high standing in the medical profession, certified by two members of the Association. The revision of the constitution includes another important change. There will be a limit on the terms of consecutive service of Councilors. While this will mean retirement, for at least a year, of valuable and experienced workers, a greater number of members will be given in rotation an opportunity to serve the Association in this capacity.

Since the organization of the American Diabetes Association, the Annual Scientific Program has been the outstanding service to physicians. This year's Program promises to equal, if not excel, those of the past. In addition, the Association took a step forward in presenting its first independent Postgraduate Course. Held in Toronto, in January, it was an outstanding success from the standpoint of both attendance and presentation.

Our Journal, *DIABETES*, is carrying on successfully, partly because of the excellent material derived from the Programs of the Annual Meeting and the Postgraduate Course. The valuable papers presented have commanded the attention of physicians interested in diabetes. In regard to future development of the Journal,

suggestions will be welcomed. Among other things, it is hoped that an active correspondence section can be established. The magazine for patients, the *A.D.A. FORECAST*, has shown a substantial increase in circulation and in serving even more successfully its readers through the information and inspiration it conveys.

This year an attempt was made to stimulate interest in diabetes among students and interns by offering a prize for the best paper on diabetes or related subjects. The sum of 250 dollars was donated by the St. Louis



FRANK N. ALLAN, M.D.
PRESIDENT, 1952-53

Diabetes Association for this purpose. The response has been gratifying; in addition to the award of the cash prize, a year's subscription to *DIABETES* will be awarded to those whose entries merit honorable mention.

Two moves involving organization have been initi-

Presented at the Banquet, 13th Annual Meeting, May 30, 1953

ated. A new Committee on Policies has been appointed to explore the further development of local Affiliated Associations and their integration into the national organization. A Conference of Delegates is meeting to discuss the various problems involved. Steps have been taken to affiliate with the International Diabetes Federation; this Federation brings together representatives of diabetes associations in many countries to serve the interests of diabetics on a world-wide basis.

A start has been made in giving direct support to research. This was named as one of the original objectives of the Association, but in the past it has received little more than moral support. Now, the Committee on Research has been given funds to establish research fel-

lowships and for grants in aid of research projects.

Financial support is needed to carry out these plans for research and to sustain the annual campaigns conducted by the Committee on Detection and Education. Diabetics have a special interest in these projects. The Council has authorized presentation of an appeal for funds in the A.D.A. FORECAST, inviting contributions to underwrite these projects of the Association. This appeal is limited; it does not represent a public, fund-raising campaign. There has already been an encouraging response.

It has been both an honor and a privilege to have had the opportunity to serve the Association as President during this year of increasing growth and new development.

Report of the Secretary, 1952-53

This Annual Report as Secretary offers a brief resume of your Association from an organizational and administrative standpoint.

As you all know, in 1940 a small group of physicians gathered together with a common interest, the subject of diabetes and all that pertains thereto, both from a clinical standpoint and a research viewpoint, to form the American Diabetes Association. From this small beginning has grown an organization of national and international reputation. This association is a medical society engaged in all of the usual functions and duties of a medical group, but in addition it is performing a national health function. The Program upon which the American Diabetes Association has launched itself is comparable in many respects to other great national health organizations. The major difference is that, unlike ourselves, others have their coffers filled with financial backing of the public, making their task much easier.

The work the American Diabetes Association has carried on, is carrying on and proposes to carry on, is done through an unusual and outstanding background of organization and administration. As a pure medical society, it has committees functioning in proper categories in the usual manner.

Ordinarily, Committees on Finance, Membership, Nomination, Constitution, Food and Nutrition, Post-graduate Education, Research, Scientific Exhibits, Scientific Programs, Scientific Publications, Statistics, Thera-

peutics, and Emergency Medical Care are common to most medical societies, large or small. It has been the duty of the Secretary, as ex-officio member of these committees, to attend and hear discussions in all Committee Meetings. I would be entirely remiss without a word of sincere and deep appreciation of the work of these various Committees. To name the Chairmen without listing the membership would be unfair, but I would like to say, not only the Chairman but each and every member attending these Committee Meetings has given of his time and thinking unstintingly and without thought of personal acknowledgment of his work. Through the foresight of the Editor, a list of all Committees, with names of members, appeared in the November-December, 1952 issue of DIABETES for our present organizational year. Without reservation, I am alert to the diligent work, cooperation and sound adjudication given to the subjects considered by them.

Certain special committees, such as the Committee on Affiliate Associations, Committee on Camps, Committee on Detection and Education, Committee on Employment and Committee on Information for Diabetics, enter into a field akin to a national voluntary health organization. In addition to these committees, the Editor and Editorial Staff of our lay magazine are to be placed in this category.

Our lay administrative staff is of utmost importance. It is necessary for you to know and appreciate it. Some four years ago our administrative staff consisted of three lay employees. Today, the work of our organization is

Presented at the Business Session, 13th Annual Meeting, May 31, 1953

carried on by twelve full-time lay employees and one part-time employee, and with the inauguration of the Annual Detection Program one to three additional lay employees are placed on the payroll. All of you who have had experience in the organization and administration of the affairs of a country or state medical society or a national organization know that the medical profession has come to rely in a large measure in its functioning and in the consummation of its programs and activities upon lay assistance. As most of you also know, lay executive secretaries or directors have become a definite part of the existence and good administration of such societies and such organizations. With a full realization of these facts your Association has established, therefore, a central office for organization and administration of the affairs of its group and is functioning in a most business-like fashion.

This in summary gives to you a brief but broad picture of the activities of your Organization from a purely administrative and organizational standpoint. We are carrying out a tremendous task. Cooperative efforts are needed. The thinking of every member and advice of every member of this Association is needed. Our Program for the future has been set by a pattern of activity of the past, but its accomplishments will depend entirely upon the goodwill of each and every member of the Association and upon a sound financial program. For continuing the work, the officers, the Council and the entire administrative force is working with diligent effort. If our accomplishments in the past are to be considered as an omen of the future, the American Diabetes Association will continue to be recognized as a great medical group.

JOHN A. REED, M.D., *Secretary*

Report of the Treasurer

This financial analysis is based on the *estimated budget* for the fiscal year 1952-53 and not on the annual statement inasmuch as not all of the auditors' figures were available at the time this report was prepared. The analysis of budgetary income and expenditure, however, may be projected to the audited statement with considerable accuracy.

INCOME

Our income can be divided into two sources: first, *earned* and second, *gifts and contributions*.

Earned income of the Association is firmly based on service to the medical profession and to the layman. Such income obviously should gradually become larger as circulation of DIABETES and A.D.A. FORECAST increases. Further, our Membership is continuing to grow and, therefore, income from this source should also increase. It is apparent, however, that there is a limit to the amount of money that can be earned through these activities and it is estimated that *earned income* will not exceed \$150,000 per annum in the next few years.

Gifts and Contributions in the fiscal year analyzed about equal the total amount of the budgetary *earned income* or, in other words, approximately one-half of the total budgetary income of \$184,775 for the fiscal

year 1952-53. Although the number of individual contributions is increasing, the major portion of gifts comes from six sources.

EXPENDITURES

The objectives of the American Diabetes Association can be simply classified in the three following categories: professional education, patient education and public education, the latter including case finding. On request, the National Office made a study of our estimated budgetary expenditures of \$176,770 for the fiscal year 1952-53 and has informed me that the estimated amount spent for each of these purposes is about equal, or a third for each. Professional education, which includes most of the Committee activities, is slightly more than the other two educational programs.

COMMENTS

Although research is one of our four major objectives, in addition to the three mentioned above, there has been no reference to it in this report. The Treasurer is aware of the attitude of the public relative to research, and a medical and health agency which does not spend a large percentage of its income for such activity is frequently held in ill favor. It is not my purpose to advocate a change in organizational policy, but rather to call the Association's attention to the fact that this matter may

Presented at the Business Session, 13th Annual Meeting

have an important bearing on our efforts to secure financial support from the public.

The Treasurer would like to compliment the Executive

Director on the efficiency and economy with which the National Office is conducted.

WILLIAM H. OLMSTED, M.D., *Treasurer*

Committee Reports

Detection and Education

Reviewing briefly, in 1948 the American Diabetes Association inaugurated the Detection and Education Program to alert the medical profession and the public to the need for early diagnosis and proper management of this ailment. Under the brilliant leadership of Dr. Howard F. Root, this annual Program was established and in succeeding years it has expanded steadily on the basis of the sound principles set forth by Doctor Root and his Committee.

As one of those basic concepts, the original Committee held that it was the responsibility of the medical profession to diagnose diabetes as early as possible. A second principle was a sound organizational plan to project this activity through County and State Medical Committees on Diabetes. With gratification, I report to you that in 1952, 63 new Committees on Diabetes were formed. This makes a total of 802 County Medical Societies and 33 State Medical Societies, members of the American Medical Association, now on record as participating in this tremendous Program of preventive medicine and education. Kentucky is the leader in this field, with 116 County Societies out of a possible 119 having formed Committees on Diabetes. In 1952, there were 44 areas of geographical participation which included 41 states, the District of Columbia, the Territory of Hawaii, Puerto Rico and Japan.

Dr. Louis H. Bauer, President of the American Medical Association, outlined a 1953 constructive nine-point program for what he called "Preservation of our American System of Medicine." His nine points were directed to all physicians and to all component societies in the American Medical Association, and I would like to quote point eight of this program, which is as follows: "Revitalize our County Medical Societies and make them leaders in their communities in all health matters." Doctor Root and his co-workers recognized that basic principle in the establishment of the Detection and Education Program. They early enlisted the assistance of the County and State Medical Societies in promulgating this

Presented at the Business Session, 13th Annual Meeting

work of the American Diabetes Association.

While this Program is annually opened with Diabetes Week, it is actually a year-round detection activity. While it is a primary responsibility of the physicians of America to undertake detection and prevention programs, a community organization under the leadership of the medical profession is needed to make this work effective. Many lay organizations and lay groups of various kinds are united under the leadership of the medical profession in detection programs at community levels.

Diabetes detection and education, sponsored by the American Diabetes Association, has led to an ever-increasing public awareness of diabetes. The impressive radio and television time and newspaper and magazine space donated to this campaign are a confirmation of civic appreciation of these efforts. The Committee on Detection and Education, as well as those who are familiar with the work, feel that it is indeed a worthwhile project and should be continued and expanded. Constant and careful examination should be made of all phases of the work with a view to improvement. Constant consideration is given to the literature promulgated by the National Office in this work, with editing and re-editing annually. The National Committee and the Association are always receptive of suggestions, advice, and critical analyses for improvement. The acceptance of our publicity, both professional and public, has been gratifying and a review of the reports and displays at the National Office is worthy of your time.

In closing this brief resume, I would call to your attention one phase of the work which is an inevitable concurrent, namely, education. It is an educational Program for the public and the profession, and this conforms to the basic concept of the American Diabetes Association. Always, effort is being made to broaden the educational value of the Program. We sincerely hope that the entire membership of the American Diabetes Association will take part in the Program at the community level and assist us in finding the unknown diabetic, educating the public in the story of diabetes,

bringing back to the fold of proper management erring diabetics and, under the guidance of the medical profession, approve, establish and assist at the community level in this splendid phase of preventive medicine.

JOHN A. REED, M.D., *Chairman*

Employment

The Committee on Employment has been in existence for five years. When originally organized by the Association, it was stimulated somewhat by requests from industry for standards regarding the employment of diabetics. This Committee's Report has been revised repeatedly. The Council, representing, as it does and should, different thoughts on diabetic control, finally reached some unanimity of opinion before the Report was released.

The Report appeared in *DIABETES*¹, and with a few minor changes is the Report which is now our accepted and standard Report.

This Committee is an unusual one in that it includes, in addition to members of the American Diabetes Association, representatives from the United States Civil Service Commission, the United Mine Workers of America, the Industrial Hygiene Foundation, and the Diabetes Section of the United States Public Health Service.

We have had contacts with the Office of Vocational Rehabilitation of the Federal Security Agency and with the Association of Railroad Engineers. We have been asked to submit standards of employability in various occupations by many groups.

It is planned that this Committee's recommendations will be circulated throughout labor and industry. In view of our present liaison, it is thought that definite cooperation will be obtained and discrimination against employment of diabetics will be greatly diminished. We have emphasized in all our communications that for a diabetic to qualify for employment, it is important that he cooperate with his physician and attempt to keep his diabetes under control at all times. It is this Committee's hope that a more realistic approach to diabetics as employees will be attained and they no longer will be classified as handicapped individuals and no longer be denied employment arbitrarily because they are diabetics.

Our contacts with labor have been most cordial, and I am sure they will cooperate in every way to see that the diabetics' working conditions are satisfactory.

Presented at the Business Session, 13th Annual Meeting

¹ Committee on Employment, American Diabetes Association: Employment of diabetics 1:336-37, July-August, 1952.

The Chairman of this Committee is deeply appreciative of the splendid cooperation we have had from these various groups whose interest in diabetes has been aroused in this question of employability of diabetics. We feel it indicates very clearly that there is a need for such joint efforts on the part of our Association, and much can be accomplished through the cooperation of our Association and the individual physicians and the various agencies which I have named.

JOSEPH T. BEARDWOOD, JR., M.D., *Chairman*

Postgraduate Education

The first Postgraduate Course, as you know, was given at the University of Toronto under Doctor Best last January, and it was an outstanding success. We set our enrollment at one hundred; due to the large number of requests and applications to take the Course, we extended it to two hundred.

The Council has approved another Postgraduate Course to be held at the Mayo Clinic in Rochester, Minnesota, January 18, 19 and 20, 1954. An important point to keep in mind here is that the registration must be kept to 125, as there will not be hotel facilities to take care of more than that. I am sorry, because I know we are going to have a large number of requests to take the Course. I am telling you now, because there will be no further announcement about this Course until approximately in September. By that time I know that we will already have had a large number of applications on file. If you or any of your friends desire to take this Course, I would suggest that you write in to the National Office promptly and have your name enrolled. We will do the best we can to take care of applicants. The Director will be Dr. Randall G. Sprague, and we hope that one of his assistants will act as an Associate Director.

EDWARD L. BORTZ, M.D., *Chairman*

Presented at the Business Session, 13th Annual Meeting.

Camps

Replies to questionnaires sent out within the past few months indicate that the nineteen camps for diabetic children in the United States and Canada accommodated, in 1952, a total of approximately 1500 children or about 200 more than during the preceding summer. This is gratifying because greater utilization of existing facilities has been one of our major objectives. There is much room for argument as to the total number of diabetic children in the country, but

there can be no doubt but that this number exceeds by several times the present capacity of existing camps which is about 2000 for the whole summer. Our problem in this regard is twofold: first, to use to the fullest the camps now established and, second, to encourage the establishment of new camps in areas now not adequately served. One must guard against setting up camps in regions in which adequate facilities already exist. The full utilization of camps now in operation depends on good professional relations, better publicity and stimulation of interest of patients and their families.

Last year saw the first year of operation of the Tennessee Camp for Diabetic Children at Sequatchie, Tennessee, under the sponsorship of the Tennessee Diabetes Association, Inc. Last summer this camp accommodated 32 children. New camps will be established this summer near St. Louis (sponsored by the St. Louis Diabetes Association, Inc.) and Portland, Oregon (sponsored by the Diabetic Children's Camp Fund). In addition, the Ottawa Branch of the Canadian Diabetes Association will operate a camp this summer; it will be administered by the Ottawa Y.M.C.A. We know also that there are interested persons in Albany and in northern New York State who would like to establish a camp upstate. Unfortunately, because of lack of facilities, the Washington Camp for Diabetic Children will be unable to operate this summer. Those in charge hope to be able to resume their work in 1954.

Various problems are constantly arising in the operation of diabetes camps. These include matters of securing funds, of publicity to insure maximal utilization and of adequate staffing both from a medical and recreational standpoint. Regarding the last-named item, there are two questions of special importance: (1) Should the American Diabetes Association or its Committee on Camps attempt to set up standards which camps should

meet in matters of medical supervision, laboratory facilities, etc., or should each camp be a law unto itself? (2) What possibility exists that hospitals and specialty boards might honor and give full credit for camp service to physicians in residencies at various hospitals? This would relieve the problem of medical staffing of camps. These and other questions are being considered by your Committee and will be discussed further at its meeting on May 31.

At present, insofar as known by the Committee, only the Illahee Lodge at Cobourg, Ontario and the Clara Barton Birthplace Camp at North Oxford, Massachusetts, have actually cared for adult diabetics except for those who might be included on the staff. Last year the Elliott P. Joslin Camp was prepared to receive men, but possibly due to inadequate publicity, not enough men applied to warrant operating the camp for them. Another try is to be made this summer. This greater use of camp facilities, by providing a week or two for adults, is well worth consideration by all those sponsoring camps. Since the investment of thought, energy and money in camps is not inconsiderable, the use of the facilities for a greater portion of the year to the benefit of adult diabetics, is certainly highly desirable.

The camping program begun in the United States has begun to spread overseas. A letter from Dr. George Constam states that last summer in Davos, Switzerland a small camp for diabetic boys was held. This will be repeated this summer on a larger and improved scale near Zurich where facilities will be set up for both boys and girls. There are those in France and Belgium who have become interested in establishing camps.

We believe that the Association may well take pride in its fostering of the Summer Camp Program. Any efforts expended are sure to yield large dividends in satisfaction and in the betterment of the welfare and future of diabetics.

ALEXANDER MARBLE, M.D., *Chairman*

Presented at the Council Meeting, May 29-30, 1953.

The Annual Meeting, May 30-31

THE SCIENTIFIC SESSIONS

The Program, which was described in a previous issue of *DIABETES*, attracted a larger audience than had registered at any previous meeting. Papers dealing with clinical and experimental subjects were received with keen interest and followed by active discussion. The

session, held jointly with The Endocrine Society, on May 30, was featured by the presentation of the Banting Memorial Lecture by Dr. Shields Warren. The two panel discussions on "The Clinical Use of Insulin," with Dr. Arthur R. Colwell as moderator, and "What It Means to Live with Diabetes," moderated by Dr. Frederick W. Williams, proved to be highly popular.

BUSINESS MEETING

At the Annual Business Meeting, held on May 31, the President pointed out the important services rendered the Association by the large number of members working on various committees. The Chairmen of the Committee on Detection and Education, the Committee on Employment and the Committee on Postgraduate Education gave brief statements; the Reports of the Secretary and the Treasurer were presented. All of these are printed elsewhere in this issue.

Dr. Howard F. Root, Chairman of the Nominating Committee, presented the following slate: President, Randall G. Sprague, M.D.; First Vice President, Henry B. Mulholland, M.D.; Second Vice President, Henry T. Ricketts, M.D.; Secretary, John A. Reed, M.D.; Treasurer, William H. Olmsted, M.D.; Councilors, for the term ending 1956, Edward L. Bortz, M.D., George M. Guest, M.D., Robert L. Jackson, M.D., Hugh Jeter, M.D., Paul Sheridan, M.D., and Frederick W. Williams, M.D. In addition, Garfield G. Duncan, M.D., was nominated to fill the vacancy on the Council which followed the election of Doctor Ricketts as Second Vice President. All were elected unanimously.

THE BANQUET SESSION

The Banquet was an occasion for sociability, as well as for consideration of serious subjects and, for the first

time, was preceded by a Social Hour. Official recognition was given to persons who had made important contributions in the service of the Association and in the advancement of medical knowledge concerning diabetes.

Dr. Frederick W. Williams, Editor in Chief of the A.D.A. FORECAST, presented to Deaconess Maude Behrman, Director of Dietetics, the Lankenau Hospital, Philadelphia, Pa., a citation which read: "To Deaconess Maude Behrman for her years of outstanding service to the A.D.A. FORECAST from the American Diabetes Association."

Dr. John A. Reed presented to Mr. Fred Allen a scroll which carried the following inscription: "In recognition of outstanding services, as an actor and humanitarian, to the Association and the American public in the cause of diabetes education and case finding through generous and unselfish participation in the Diabetes Detection Drives in recent years." Mr. Allen, responding in his usual inimitable style, presented a discourse on the practice of medicine from his point of view which was considered by many of those present to be one of his best performances.

Mr. William F. (Bill) Talbert was presented a silver tray by Dr. Randall G. Sprague as a token of appreciation from the Association for his many services during past years; particularly his tennis tour last fall during Diabetes Week, when he played exhibition matches in nine cities in nine days from Coast to Coast.

The Address of the President included his report on



RECIPIENTS OF THE BANTING MEDAL POSE WITH DOCTOR BEST. FROM LEFT TO RIGHT ARE DRs. FRANK N. ALLAN, SHIELDS WARREN, CHARLES H. BEST, WALTER R. CAMPBELL AND ALMON FLETCHER.

"The State of the Association" (printed elsewhere in this issue) and a discussion of the "Psychology of Diabetes."

Dr. Shields Warren, who had earlier delivered the Banting Lecture at the Scientific Session, spoke on "Atomic Energy in Relation to Medicine." The President then presented him with the Banting Medal.

Prof. Charles H. Best described the important work of Drs. Walter R. Campbell and Almon Fletcher in the first clinical trials of insulin, in recognition of their pioneer clinical research, and presented the Banting Medal to each.

The immediate Past President, Dr. Arthur R. Colwell, made the presentation of the Banting Medal to Dr. Frank N. Allan, referring to his presence as a medical student in Toronto at the first treatment of a human diabetic with insulin, the opportunity given him to participate in the early research of insulin under Prof. J. J. R. Macleod, his later association with Dr. Russell M. Wilder at the Mayo Clinic, with whom he reported the first case of hyperinsulinism found to be due to an islet tumor of the pancreas, his present work as Executive Director of the Medical Department of the Lahey Clinic in Boston, and his services to the Association as Editor of *DIABETES* and as an officer of the organization.

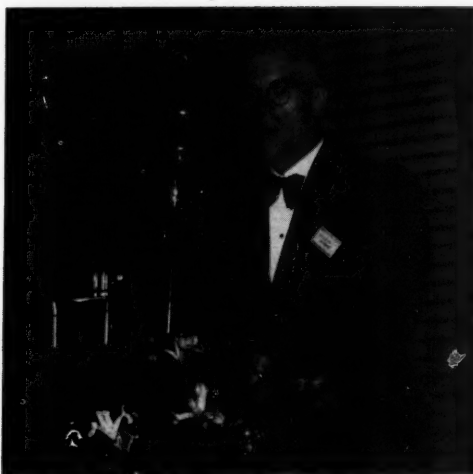
PRESENTATION OF BANTING MEDAL TO DR. SHIELDS WARREN

Remarks of Dr. Frank N. Allan

The Banting Lecturer for 1953 is a man whose name is well known for his work in the field of the pathology of diabetes.

His career as a pathologist began immediately after graduating from Harvard Medical School in 1923, and two years later he became a member of the teaching staff. For five years he has held the rank of Professor of Pathology in Harvard Medical School. He became the pathologist of the New England Deaconess Hospital in 1927, and thus for over a quarter of a century he has had an unusual opportunity to study the problems of diabetes through his association with Doctor Joslin and others in a hospital in which there is an unusual concentration of interest in diabetes. He is the author of a book *The Pathology of Diabetes*, which is now in its third edition. He is also a co-author of books dealing with neuropathology and the cytopathology of cancer.

He was on active duty in the U. S. Navy for three and a half years. He was chief of a medical field team of a U. S. Naval Technical Mission to Japan in the fall



DR. SHIELDS WARREN DELIVERING THE BANTING MEMORIAL LECTURE DURING THE 13TH ANNUAL MEETING.

of 1945 and executive officer of the Naval Medical Research Section at the first post-war atomic tests (Operation Crossroads). Since then he has served the Government as a civilian in numerous capacities. He was director of the Division of Biology and Medicine of the U. S. Atomic Energy Commission from 1947 to 1952. He has also served as a consultant to several agencies.

At present, he is chief consultant in Atomic Medicine to the Department of Medicine and Surgery of the Veterans Administration, member of the Council of Central Office consultants of the Veterans Administration, Senior Civilian Scientist in the Bureau of Medicine and Surgery, U. S. Navy, to evaluate work in radiobiology; member of the Scientific Advisory Board to the Chief of Staff, U. S. Air Force, and National Consultant to the Air Force.

He has been an officer of several medical organizations and has received various honors including the American Cancer Society Medal for 1950. In the current year he has been given an award by the Board of Editors of *Modern Medicine* and he has also received the William Proctor Award for Scientific Achievement from the Scientific Research Society of America for distinguished achievement in the progress of medicine as exemplified by his development of a peace-time program for the use of atomic energy and radioactive isotopes in biology and medicine.

Both of these recent awards were given because of the high merit of his work in a field unrelated to diabetes. I have, therefore, asked him to tell us about "Atomic Energy in Relation to Medicine," a subject of keen in-

terest to the medical profession and the general public.

It gives me great pleasure to present to Dr. Shields Warren, on behalf of the American Diabetes Association, the Banting Medal in recognition of his achievements in relation to diabetes.

PRESENTATION OF BANTING MEDALS TO DOCTORS CAMPBELL AND FLETCHER

Remarks of Prof. Charles H. Best

Our President has given me the honor of presenting two very distinguished clinicians—Dr. Walter R. Campbell and Dr. Almon Fletcher of Toronto—for the award of Banting Medals from the American Diabetes Association.

As you will all appreciate, Doctor Campbell and Doctor Fletcher are old and very highly valued friends of mine. When the stage was reached in the development of insulin which justified its trial in human patients, these were the two internists who were given the great responsibility for the clinical investigation of the anti-diabetic hormone.

In preparation for this moment, I have read again the original clinical reports of Doctor Campbell and Doctor Fletcher with the late Fred Banting. It is amazing to realize how many presently established clinical procedures were reported for the first time in those papers—the dosage and timing of insulin, the route of administration, the treatment of diabetic coma with insulin, the treatment of insulin hypoglycemia and many other great problems which were successfully attacked. Banting was by nature a healer of the sick and, while he debated with himself whether or not he should leave our experimental studies, the attraction of the clinical application was so great that, as you know, he did for a time participate in the early clinical use of insulin. But the main responsibility for the selection of patients, and for the details of the clinical methods employed, was born by these two with the advice and help of the head of their department, Professor Duncan Graham.

I can well remember with what keen interest Banting and I awaited the reports of comments on the first clinical findings. We did not have to wait for publications because our Insulin Committee invited a group of distinguished United States clinicians to come to Toronto. These were: Drs. Frederick M. Allen, Elliott P. Joslin, Russell M. Wilder, Rollin T. Woodyatt, John R. Williams and H. R. Geyelin. I shall not attempt to describe the first of these meetings, which I remember very vividly, further than to say that the clinical results obtained by

Campbell and Fletcher were confirmed with no essential modifications by the clinicians in this country and, indeed, a little later by clinicians the world over.

President Allan wrote to me to ask me to say something about the early preparation of insulin, but I would prefer not to spend much time on that subject because my pleasure and duty this evening is the presentation of these two world-famous physicians. Banting and I were anxious that the first insulin used clinically should be made in our own small laboratory and this, indeed, was the case. The insulin was not very potent by present standards, and there were plenty of impurities in it but it had, however, caused a dramatic reduction in the blood sugar of a diabetic dog, and Banting and I went through the ceremony of injecting the material into ourselves. It was made from normal beef pancreas by alcoholic extractions and subsequent removal of fat. Dr. J. B. Collip, who joined us in the autumn of 1921 with the objective of purifying our crude insulin, had been given the information which we had available. We knew that insulin could be extracted from normal beef pancreas with 65 per cent ethyl alcohol. We knew that it was not soluble in certain fat solvents. Dr. Collip did a fine piece of work in the further purification of the material. But there were, of course, plenty of things that none of us knew at that time and some of these, such as the insolubility of insulin in water around pH 5 and its absorbability on almost anything it touched, particularly at that pH, were the main difficulties which prevented us from making adequate amounts of insulin for clinical use at that time.

Professor Collip left Toronto to return to his post in Alberta while some of the earliest patients were receiving their first insulin. Before he left, great difficulty had been encountered in repeating the early larger scale experiments and in securing enough insulin to carry on treating even the few patients. When Collip left, I found myself forced back from the physiological problems I had chosen to attack into the preparation of insulin and, as I have said on several occasions before, those were the most hectic days through which I have lived. There was no opportunity to stand back from the problem and look at it carefully and scientifically. One or two of the patients who had been rescued with insulin actually succumbed from lack of it. To make a long story short, we did improvise wind tunnels heated by open electric elements to blow off the acetone and concentrate small amounts of insulin for clinical use. These struggles in the Connaught Laboratories, in the University of Toronto, and the early large-scale operations

of Eli Lilly and Company, make interesting scientific history, but these are not the points on which I wish to concentrate your attention now.

You will all share my conviction that Dr. Walter R. Campbell and Dr. Almon Fletcher have placed the whole medical world in their debt, by the great skill and care with which they carried out the pioneer clinical investigations which were a necessary preliminary to the application of insulin for the treatment of diabetes mellitus in all parts of the world.

I have the very greatest pleasure, Mr. President, in presenting for the award of the Banting Medal—Walter Ruggles Campbell, B.A. 1911, M.A. 1912, M.B. 1915, M.D. 1917 (University of Toronto); F.R.C.P. (C) 1930; F.R.S.C. 1933; Canadian Army Medical Corps 1917-1919; member of staff of Department of Medicine, University of Toronto, and Medical Service, Toronto General Hospital, 1919; Associate Professor, Department of Medicine, University of Toronto; Senior Physician, Toronto General Hospital, 1948.

I also present Andrew Almon Fletcher, M.B. (University of Toronto) 1913; F.R.C.P.(C) 1930; Canadian Army Medical Corps (overseas) 1915-1918; member of the staff of Department of Medicine, University of Toronto, and Medical Service, Toronto General Hospital; retired in 1951. Assistant Professor, Department of Medicine, University of Toronto, and Senior Physician, Toronto General Hospital, 1922-1951; in charge of the Clinical Investigation Unit, Sunnybrook Hospital (Department of Veterans Affairs), Toronto, 1951.

CONFERENCE OF DELEGATES OF AFFILIATE ASSOCIATIONS

Fifty-seven representatives of 26 of the 33 Affiliate Associations and nine areas forming Affiliates met in New York City on Monday, June 1, 1953 for the third annual Conference of Delegates of the Affiliate Associations.

Dr. Lester J. Palmer of Seattle, Washington, Chairman of the Committee on Affiliate Associations, re-emphasized four points of policy as stated at the 1952 Annual Meeting of the Association in Chicago. In Doctor Palmer's words:

"1. The organizing committees of Affiliates are to be composed of a majority of physicians, with preferably a majority of these physicians being members of the American Diabetes Association.

2. Each Affiliate will designate a geographical area which it is to serve.

3. Each Affiliate is to incorporate under the laws of the state in which it is located.

4. Each Affiliate must express its willingness to operate within the policies and purposes of the American Diabetes Association."

Based on these policies, the chief topic considered by the Conference was that of the evolving relationships between Affiliates and the National Association. Dr. Edwin L. Rippy of Dallas, Vice Chairman of the Committee on Policies, presented a plan with an organizational chart which was part of a report of that committee and accepted by the Council at its meeting a few days previously. The proposal, which included the creation of a Board of Governors based on state representation, was studied in small conference groups. The proposal also recommended appointing of Delegates, from both the Clinical and Lay Societies of each Affiliate, forming a House of Delegates. The Governor would serve as Senior Delegate in the House and that body would function in an advisory and planning capacity to the Council in matters primarily affecting the Affiliates.

There was also considerable discussion about the increasing problem of securing adequate financial support for the activities of the National Association. The possibility of developing such support through membership dues from individual members of Clinical and Lay Societies of Affiliates as well as by other means was considered. Attention was further given to the role of laymen in the future of the Affiliate Association Program.

In closing, the Conference unanimously adopted the proposal that Governors be appointed representing each state and urged that such appointments be made by the Association's Council as soon as feasible.

PUBLIC MEETING

An overflow crowd estimated at more than 1,300 persons participated in a Public Meeting held on the evening of June 1, 1953, in the beautiful Century Room of the Hotel Commodore in New York City. Sponsored jointly by the Lay Society of the New York Diabetes Association and the American Diabetes Association, the meeting honored Dr. Charles H. Best of Toronto and heard Dr. Randall G. Sprague of Rochester, Minnesota, newly-elected President of the National Association, speak on "The Art of Living with Diabetes."

Doctor Best was presented with a silver tray by Mr. Richard Porter, on behalf of the New York Association's Lay Society, as a token of appreciation from those whose survival had been made possible by the discovery of insulin by Doctor Best and Sir Frederick G. Banting. For the National Association, Doctor Sprague received from Dr. August L. Beck of New Rochelle,

ORGANIZATION SECTION

N. Y., a plaque honoring "Marjorie," the thirty-third and last in the series of dogs used in the experimental work which lead to the discovery of insulin.

With Dr. Frank N. Allan of Boston, retiring President of the American Diabetes Association, as moderator, a panel of physicians then discussed questions previously submitted by those attending the meeting. Included on

the panel were Arthur R. Colwell, M.D., of Chicago; Lester J. Palmer, M.D., of Seattle; Edwin L. Rippy, M.D., of Dallas, and Howard F. Root, M.D., of Boston.

The Chairman of the Lay Society, Mr. Leroy Plath, presided and subsequently reported that as a result of the meeting 52 subscriptions to the A.D.A. FORECAST were secured and 86 individuals joined the Lay Society.



DR. CHARLES H. BEST, LEFT, IS PRESENTED WITH A SILVER TRAY BY RICHARD PORTER ON BEHALF OF THE NEW YORK DIABETES ASSOCIATION'S LAY SOCIETY, AS DR. RANDALL G. SPRAGUE LOOKS ON.

ASSOCIATION NEWS

SECOND POSTGRADUATE COURSE, JANUARY 18-20, 1954

At the Business Session of the Thirteenth Annual Meeting, Dr. Edward L. Bortz, Chairman of the Committee on Postgraduate Education, announced (see Organizational Section, page 334) in the Report of his Committee that plans had been completed to hold the second Postgraduate Course at Rochester, Minnesota, January 18-20, 1954. The Course will be under the co-directorship of E. H. Ryneason, M.D., and Randall G. Sprague, M.D., both of whom are Professors of Medicine, Mayo Foundation, University of Minnesota, and Consulting Physicians, Division of Medicine, Mayo Clinic, Rochester, Minnesota.

In spite of the fact that the maximum number of registrants for the first Course was doubled (to nearly two hundred) shortly before the Course was held, it was necessary to return 86 applications for registration because of limited facilities. Registration for the second Course will be restricted to 125. A number of registrations already have been received and, therefore, members of the Association and other members of the medical profession interested in the Course are urged to make their reservations at once. Preference will be given to those whose applications could not be accepted last year and, of course, to Association members.

Registration fee for the three-day Course: \$40 for members; \$75 for non members. Applications for registration should be sent to J. Richard Connelly, Executive Director, at the National Office.

The Program will be announced in an early issue of *DIABETES*, and Preliminary Programs will be sent directly to the membership.

1954 AWARD FOR BEST PAPER ON DIABETES BY MEDICAL STUDENTS AND INTERNS

Considerable interest was expressed in the competition for the Award this year to medical students and interns for the best paper in the field of diabetes and basic metabolic problems. The name of the winner, as well as the names of the authors whose papers will receive honorable mention, will be announced in a future issue of *DIABETES*.

Another Award will be made in 1954, and Association members and subscribers to *DIABETES* are urged to encourage medical students and interns in their schools and hospitals to submit papers as early as possible.

Candidates may select any subject related to diabetes. The paper can be a report of original studies, a biographical or historical note, a case report with suitable comment or a review of the literature. The length may be from six to eighteen pages, typewritten with double spacing.

Manuscripts should be submitted by April 1, 1954, to the Editorial Office of *DIABETES: The Journal of the American Diabetes Association*, 11 West 42nd Street, New York 36, N. Y. The papers will be reviewed by the Editorial Board, which will take into consideration the value of the material and method of presentation, in selecting the best paper.

The Prize of \$250 again is made possible by the generosity of the St. Louis Diabetes Association.

REVISED REQUIREMENTS FOR ASSOCIATION MEMBERSHIP

The Council, at its Annual Meeting, on May 29-30, adopted a revised Constitution and By-Laws, as recommended by the Committee on Constitution, under the chairmanship of Dr. Henry T. Ricketts, which became effective June 1, 1953.

Plans are going forward to reprint this new document for distribution to the membership, possibly in conjunction with a Directory of Members. Both are scheduled to be off the press in the early fall.

One of the important revisions of the By-Laws was to liberalize the qualifications for Active membership in the Association, as follows:

BY-LAWS—ARTICLE I—MEMBERSHIP

Section 1. Classes of Members . . .

1. Active Members. Persons eligible for election to this class shall be
 - a. Graduates of medical schools approved by the Council on Medical Education of the American Medical Association; and
 - b. Other physicians and scientists interested in diabetes who, in the judgement of the Council, possess appropriate qualifications.

Subscribers to this publication who are not members of the Association may secure application forms from the National Office, and members are encouraged to ask their colleagues who are interested in the field of diabetes to join the Association. Associate membership

is available to those in the allied fields, such as dietetics, nursing, medical technology, physiotherapy and so forth.

OPENING OF A CLINICAL CENTER, NATIONAL INSTITUTES OF HEALTH

On July 2, the 64 million dollar, 14-story Clinical Center of the National Institutes of Health, at Bethesda, Maryland, was dedicated. The building includes a 500-bed hospital and 1100 scientific laboratories. It is completely air-conditioned and contains the latest equipment for comfort and research.

The dedication ceremony was opened by Dr. Leonard A. Scheele, Surgeon General, Public Health Service, and Dr. W. H. Sebrell, Jr., Director, National Institutes of Health. The dedication address was given by the Honorable Oveta Culp Hobby, Secretary of Health, Education and Welfare. After the ceremony, the building was opened for inspection.

Among the members of the Association known to be present at the ceremony were Drs. Joseph H. Barach of Pittsburgh, Samuel Benjamin of Washington, D.C., Edward L. Bortz of Philadelphia, and Willoughby J. Rothrock of Washington, D.C. The Association was represented by Dr. John A. Reed, Secretary, and Mr. J. Richard Connelly, Executive Director.

BINDERS FOR "DIABETES" NOW AVAILABLE

Attractive binders for both the 1952 and 1953 issues of *DIABETES* are available for immediate shipment. The insert binder, made by a nationally known company, is sturdy, attractive and will hold six issues, forming one volume. The cover is semi-flexible blue grain with gold lettering. Readers are urged to take advantage of the current low price of \$2.00 per binder; costs may increase in the future.

CLINICAL NEWS FROM AFFILIATE ASSOCIATIONS

CLEVELAND DIABETES SOCIETY: A dinner was held on Friday evening, May 22, at Wade Park Manor. Dr. J. Bornstein of the Baker Medical Research Institute, Melbourne, Australia, was the guest speaker. His talk was on "Studies on Plasma Insulin." Doctor Bornstein has spent the last eighteen months at Washington University, St. Louis, working with Dr. Carl Cori.

WASHINGTON DIABETES ASSOCIATION: A combined meeting of the lay and clinical societies was held in the Auditorium of the School of Medicine of the University of Washington on Friday, June 26. Three hundred attended the meeting and heard a discussion on current research in the field of diabetes by Robert H. Williams, M.D., Professor of Medicine of that school. Employ-

ment problems confronting diabetics were discussed by Dr. Thrift G. Hanks of the Boeing Airplane Company. Dr. R. H. Barnes, President of the Clinical Society, and Mr. S. Ross Pond, Field Representative of the American Diabetes Association, discussed organizational problems. Sixty new members to the Lay Society were enrolled at the meeting, and thirty A.D.A. FORECAST subscriptions were received.

IOWA PASSES LAW RE LABELING OF ARTIFICIAL SWEETENERS

The Journal of the American Medical Association reported on May 30 that the Iowa State Legislature, on April 29, 1953, approved Bill No. S 205. This provides "that where any artificial sweetening product such as saccharine or sulfamate is used by any person in the manufacture or sale of any article of food intended for human consumption, the container in which any such food or beverage is sold shall be clearly labeled with the name of the sweetening product used and the portion of the store where such food or beverage is displayed shall be identified by an appropriate sign, reading 'Food for Dietary Purposes.'"

RESEARCH FUNDS FOR THE NATIONAL INSTITUTES OF HEALTH

The eight Advisory Councils of the National Institutes of Health recently established a new record in approving 1,698 applications for research grants, totaling \$17,800,137. One hundred and seventy-one applications, amounting to \$1,675,105, were approved in the field of arthritis and metabolic diseases. More than one-half of the total applications were continuation grants.

The U. S. Senate Appropriations Committee recommended an added \$15,800,000 increase to President Eisenhower's recommended \$56,300,000 for support of research for the National Institutes of Health and their component organizations. Allocation for the National Institute of Arthritis and Metabolic Diseases was increased to \$7,000,000.

NEW MEMBERS

The following Active Members were elected as of June 30, 1953:

ARIZONA

Baritell, Harriet	Tucson
Mayer, Hyman	Tucson
Robbins, Clarence L.	Tucson
Williams, Marguerite S.	Tucson

CALIFORNIA

Amatuzio, Donald S.	San Leandro
Elden, Harold	El Cajon
Solomon, David H.	Los Angeles

ASSOCIATION NEWS

FLORIDA

Thompson, Ronald MacKinnon West Palm Beach

ILLINOIS

Baumeister, Carl F. Berwyn

MICHIGAN

Newcomb, Arnold B. Berkley

NEBRASKA

Gathman, Leroy T. South Sioux City

NEW JERSEY

Lipton, Louis Passais

NEW YORK

Bight, Curtis P. Kingston

Guillemont, Grant Niagara Falls

Henderson, William W. Niagara Falls

Iannuzzi, Peter J. Niagara Falls

La Tona, Salvatore R. Niagara Falls

McDermid, William J. Niagara Falls

Palumbo, Frank J. Niagara Falls

Pellicano, Victor L. Niagara Falls

Vickers, William H. Niagara Falls

Welch, Lauren G. Niagara Falls

Lau, Kimm-Chan K. New York

OHIO

Bowers, Donald F. Columbus

Clark, Charles M. Akron

Lamanna, John R. Youngstown

OREGON

Woodard, Don W. Salem

PENNSYLVANIA

Wing, Raymond Easton

TEXAS

Roberts, Walter D. Austin

VERMONT

Eddy, Winston M. Burlington

WISCONSIN

Belfus, Frank H. Milwaukee

Van Fleet, Mary E. Milwaukee

ARGENTINA

Schor, Isaias Buenos Aires

CANADA

Feller, Jacob Ottawa

Hall, William E. Toronto

Laroche, Louis N. Quebec

McGarry, Eleanor E. Montreal

Saibel, David Montreal

Rusted, Ian E. St. John's,

Newfoundland

Symposium on Diabetes, New York, October 8

NEW YORK DIABETES ASSOCIATION: The "First Symposium Day on Diabetes" will be held on Thursday, October 8, in the Auditorium, Memorial Center for Cancer and Allied Diseases, 410 East 68th Street, New York City. The Course will consist of "authoritative summaries and reviews of current research in the field of diabetes and general metabolism with application to the practice of medicine."

The morning program:

Presiding: Irving Graef, M.D., Chairman, Professional Education Committee.

(20-Minute Papers—10-Minute Discussions)

The Hereditary Obese Hyperglycemic Syndrome in the Mouse, Jean Mayer, Ph.D., D.Sc., Assistant Professor of Nutrition, Department of Nutrition, Harvard School of Public Health and Department of Physiology, Harvard Medical School, Boston, Mass.

Lipogenesis in Experimental Diabetes, Samuel Gurin, Ph.D., Professor of Physiological Chemistry, University of Pennsylvania, School of Medicine, Philadelphia, Pa.

Hormonal Control of Carbohydrate Metabolism, C. N. H. Long, M.D., Sc.D., Sterling Professor of Physiological Chemistry, Yale University, School of Medicine, New Haven, Conn.

The Action of Insulin, W. C. Stadie, M.D., John Herr Musser Professor, Department of Research Medicine, University of Pennsylvania, Philadelphia, Pa.

The Hyperglycemic Factor, Gerald A. Wrenshall, Ph.D., Banting Institute, University of Toronto, Toronto, Ontario, Canada.

Insulin and Complications of Diabetes—Endogenous and Exogenous Insulin, Herman O. Mosenthal, M.D., Past President, New York Diabetes Association, American Diabetes Association.

The afternoon program:

Presiding: Robert Goodhart, M.D., Chairman, Committee on Research.

Disturbances in the Metabolism of Vitamin B-12 in Diabetes and Their Significance, Bacon Chow, Ph.D.,

Associate Professor, Johns Hopkins University, School of Public Health and Hygiene, Baltimore, Md.

Indications for the Use of Various Insulins, Franklin B. Peck, M.D., Director, Medical Division, Eli Lilly and Company, Indianapolis, Ind.

The Management of Diabetes During Pregnancy, David Hurwitz, M.D., Chief, Diabetes Service, Boston City Hospital; Chief, Division of Medicine, Mt. Auburn Hospital, Boston, Mass.

The Management of Emotional Factors in Diabetes, Lawrence Hinkle, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College, New York, N. Y.

The Use of Proteolytic Enzymes in the Management of Diabetic Ulcer, W. Ross McCarty, M.D., Associate Professor of Surgery, New York University—Bellevue Medical Center of New York University College of Medicine.

The Nutritional Management of Diabetes, Herbert Pollack, M.D., Ph.D., Associate Physician, Metabolic Diseases, Mt. Sinai Hospital, New York, N. Y.

The Meeting will be followed by a Dinner at 7:15 p.m., preceded by a Reception at 6:30 p.m. at the New York Academy of Sciences, 2 East 63rd Street, New York City. Frederick W. Williams, M.D., Chairman of the Clinical Society, will preside, and Herbert Pollack, M.D., Ph.D., Chairman, Symposium Day Committee, will introduce the guest speaker, J. S. L. Browne, M.D., Ph.D., Director, University Clinic, Royal Victoria Hospital, Montreal, whose discussion will be on "Certain Concepts and Difficulties in Clinical Endocrinology."

There is no charge for the Course but advanced registration is required. Dinner reservations are available at \$6 per person. Reservations for both should be made through Mr. T. L. Kingsley, Executive Officer of the New York Diabetes Association.

PERSONAL

Dr. Russell M. Wilder retired as Director of the National Institute of Arthritis and Metabolic Diseases on July 1. Internationally known for his contributions to knowledge in the fields of diabetes, metabolism and nutrition, Dr. Wilder was President of the American Diabetes Association in 1946-1947. He has returned to his home in Rochester, Minnesota, to live quietly in the pursuit of his several hobbies.

The Chicago Society of Internal Medicine, at its recent Annual Meeting, elected Arthur R. Colwell, M.D. Vice President.

George M. Guest, M.D. of Cincinnati was elected

first President of the Inter-American Foundation for Postgraduate Medical Education. The Foundation was organized to encourage the exchange of postgraduate students and research workers in medicine and allied fields of science in South and North American countries. The proposed program of that organization also provides for interchanges of visiting lecturers. Expenses will be defrayed through the Foundation.

The National Vitamin Foundation announced that Elaine P. Ralli, M.D., of New York University College of Medicine, received a grant on June 30, 1953 for studies of the influence of certain nutritional fractions in patients with diabetes mellitus.

